CONSERVATION OF MECHANOSIGNALING: RESPONSES OF HUMAN ADULT MESENCHYMAL STEM CELLS AND DIFFERENTIATED VASCULAR CELLS TO APPLIED PHYSICAL FORCES

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CONSERVATION OF MECHANOSIGNALING:
RESPONSES OF HUMAN ADULT MESENCHYMAL STEM CELLS AND DIFFERENTIATED VASCULAR CELLS TO APPLIED PHYSICAL FORCES

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LIST OF SYMBOLS OR ABBREVIATIONS

Cox2	prostoglandin synthase 2, a.k.a. Cox-2, gene.
CVD	cardiovascular disease.
ECs	human aortic endothelial cells.
eNos	endothelial nitric oxide synthase, a.k.a. Nos3, gene.
EPC	endothelial progenitor cell.
ESC	embryonic stem cell.
GvHD	graft versus host disease.
Hmox1	heme oxygenase 1 gene.
Il8	interleukin 8 gene.
Klf2	Kruppel-like factor 2 gene.
Mcp1	monocyte chemotactic protein 1 gene.
MI	myocardial infarction.
MSCs	human adult bone marrow-derived mesenchymal stem cells.
Pecam1	platelet endothelial cell adhesion molecule 1, a.k.a. CD31, gene.
SMCs	human aortic smooth muscle cells.
Vcam1	vascular cell adhesion molecule 1 gene.
VE-Cad	vascular endothelial cell adhesion molecule, a.k.a. CD144 or Cadherin 5, gene.
vWF	von Willebrand factor gene.

SUMMARY

Mesenchymal stem cells (MSCs) may benefit vascular cell-based therapies as smooth muscle or endothelial cell substitutes or through paracrine actions to repair, replace, or regenerate vascular tissue. Previous studies have demonstrated that MSCs can adopt traits of smooth muscle cells (SMCs) or endothelial cells (ECs), as well as secrete specific factors that tune signaling and material properties in the local environment. Few studies have investigated the cell signaling response of MSCs to mechanical forces present in the vasculature: specifically, shear stress due to blood flow and cyclic strain due to pulsatile blood flow. Thus, the central objective of this dissertation was to determine the signaling responses of MSCs to vascular-relevant applied physical forces, in comparison with that of differentiated vascular cells.

Vascular-relevant mechanosignaling of MSCs was assessed through two comparisons: (1) MSC and SMC responses to applied cyclic strain and (2) MSC and EC responses to applied fluid shear stress. MSCs and SMCs were seeded on fibronectin-coated silicone and subjected in vitro to cyclic strain (10%, 1 Hz) or parallel static culture using a custom-built equibiaxial cyclic strain device. Gene expression analysis of 84 signal transduction molecules demonstrated both cell types respond with significant ($p < 0.05$, n=3) fold-changes ($|FC| \geq 1.5$) within 24 hours of applied equibiaxial strain. Most strain-responsive genes identified were significantly strain-responsive in only one cell type. A signaling trio of Interleukin 8, Vascular cell adhesion molecule 1, and Heme oxygenase 1 was significantly altered in both MSCs and SMCs, suggesting cyclic strain regulates immune and inflammatory functions in both cell types. The response to shear stress of MSCs and ECs was compared using cells seeded on type I collagen or fibronectin and exposed to steady laminar shear stress (5 or 15 dyn/cm^2) using a parallel plate shear chamber system. Gene expression was compared in MSCs and ECs for a panel of immune and inflammation-related markers. Expression of Cox-2 and Hmox-1 increased significantly

($p < 0.05$, n3; $|FC| \geq 1.5$) in both cell types. Reduced shear stress-responses of Mcp-1, Pecam-1, and VE-Cad in MSCs relative to ECs suggests that MSCs promote less inflammation and immune activation in response to shear stress than ECs. Mechanosensitivity profiles for MSCs and differentiated vascular cells were broadened using whole genome microarrays. These high-throughput studies confirmed that (1) signaling profiles between sample groups vary significantly more ($p < 0.05$, n=3) with cell type than applied force condition and (2) a subset of conserved mechanosensitive genes alter expression levels significantly and in the same direction fold-change in multiple cell types. Bioinformatics analysis of these conserved mechanoresponsive genes highlighted oxidative stress, cell cycle, and DNA replication as functions regulated by vascular-relevant mechanical cues.

These studies demonstrate that MSCs partially reproduce differentiated vascular cell mechanosignaling, while simultaneously altering expression of genes not typically force-responsive in vascular cells. This work defines a role for conserved mechanosignals, based on genes whose expression in response to applied force alters significantly ($p < 0.05$, $n \geq 3$) and by at least 1.5-fold change in multiple cell types and/or force types. Comparisons completed for this dissertation motivate future studies to track the functional impact of specific similar or unique MSC mechanoresponses. This work contributes to design of MSC-based vascular therapies and an understanding of stem and differentiated cell mechanobiology.

CHAPTER I

INTRODUCTION

Cardiovascular disease continues to be the primary cause of death in the U.S. each year [319]. Treatment of cardiovascular disease (CVD) is limited by our ability to replace, regenerate, or repair the native, physiological function [79]. Stem cell-based therapies offer one way to improve on this, using biological mechanisms to treat cardiovascular disease [226, 14, 217]. Several groups have investigated various types of stem cells for treatment of CVD, often focusing on either differentiation to generate a new source of vascular cells or repair of specific functions (e.g., ejection fraction improvements after myocardial infarction, MI) [87, 48]. Little is known about the vascular-relevant mechanosensitivity of stem cells, although mechanical cues are inherent in the vasculature and affect signaling in endothelial and smooth muscle cells [158, 74, 89]. The **central objective** of this work is to investigate the effects of physiologically-relevant mechanical cues on mesenchymal stem cell signaling, one of the most promising stem cell sources for cardiovascular therapies.

1.1 Significance of Research

Mechanical forces are an inherent component of the microenvironment to which cells are exposed, both in vivo and in vitro. This dissertation contributes to rational design of tissue engineered and regenerative medicine therapies by providing (a) knowledge of the cell signaling response of MSCs to cardiovascular-relevant applied physical forces and (b) comparison of MSCs response with that of cells normally found in the vasculature. Very limited data exists describing the force-sensitivity of stem cells, specifically MSCs. Execution of the specific aims in this dissertation provides data relevant to basic stem cell, particularly MSCs, biology. Though motivated in the context of vascular therapies, this work can also benefit other applications in which cyclic strain and/or shear stress are relevant. In terms of fundamental mechanobiology, these aims provide a systematic analysis of mechanical

responses in three cell types. The high-throughput approach may provide a framework for future mechanoresponse studies. Furthermore, these in vitro cell culture systems may serve as models of biological response in which to study development, disease, and potential therapeutics. Finally, this data set describing the signaling pathways active at different stages of differentiation may be relevant to the field of developmental biology, given the importance placed on understanding and controlling cellular differentiation.

1.2 Clinical Significance

Data from the Centers for Disease Control and Prevention ranks cardiovascular disease as the number one cause of death in the United States [319]. Heart, cerebrovascular, and hypertension-related diseases accounted for 32% of all deaths in 2007, according to the most recent data available from the CDC [319]. More than 25 million people (1̃2% of the adult population) in the US are non-institutionalized victims of heart disease [227] and 27% of persons aged 20 years and older have hypertension [33], a disease specifically related to the vasculature. In 2007, care of cardiovascular diseases in the U.S. is projected to require more than $400 billion in direct healthcare and related morbidity/mortality costs [198]. Advances in treatment options for cardiovascular diseases are needed to reduce both the number of patients affected and the associated economic burden. Cell-based therapies are one proposed method by which to use biological mechanisms of action to promote health [122]. Mesenchymal stem cells, a bone marrow-derived adult progenitor cell source, are currently involved in more than 85 clinical trials world-wide listed in the NIH clinical trials database [197] and are reported in several published trial results [91, 150, 275, 11, 38, 39, 127, 128, 164].

1.3 Overview of Dissertation Approach

Mesenchymal stem cells (MSCs) may benefit vascular therapies through paracrine action or potentially differentiation along vascular lineages. In spite of clues that MSCs may ameliorate vascular problems, we lack broad and predictive understanding about MSCs signaling in the vascular environment. To address this knowledge gap and expand knowledge

of vascular cell mechanoresponse, parallel comparisons for MSCs and differentiated vascular cells have been completed. Our **central hypothesis** is that cell signaling changes in response to applied physical force are conserved between MSCs and differentiated cells. The MSCs mechanoresponse was compared to endothelial cells exposed to steady laminar fluid shear stress and to vascular smooth muscle cells exposed to equibiaxial cyclic strain. Signaling was assessed using either a panel of related markers under a range of force conditions or using microarrays for high-throughput signaling analysis under a single shear stress or strain condition. Three specific aims, represented in Figure 1 and described below, were completed to address the central hypothesis.

1.3.1 Specific Aim 1.

Determine the mechanoresponse, in particular Interleukin 8 signaling, of MSCs and aortic smooth muscle cells (SMCs) as a function of equibiaxial cyclic strain. The *working hypothesis* is that Interleukin 8 will be activated in response to cyclic strain in both MSCs and SMCs. MSCs and SMCs were exposed to equibiaxial cyclic strain (10%, 1 Hz) for 24 hours and assessed using PCR arrays for expression of signal transduction genes. Novel strain responsive genes, unique to a single cell type or present in multiple cell types, were identified using significance and fold change criteria. A strain-responsive signaling motif, including Interleukin 8, was identified from PCR array analysis. Kinetics (0-24 hr) of strain-response for genes in this signaling node were quantified in MSCs and SMCs using standard qPCR. Results are described in Chapter 3.

1.3.2 Specific Aim 2.

Determine the inflammatory and immune mechanoresponses, specifically Pecam1 signaling, of MSCs and aortic endothelial cells (ECs) as a function of steady laminar shear stress magnitude and duration. The *working hypothesis* is that Pecam1 gene and protein expression will increase in response to shear stress in both MSCs and ECs. MSCs and ECs were subjected to varying durations (0-48 hr) of steady laminar fluid shear stress at a low (5 dyn/cm^2) or high (15 dyn/cm^2) magnitude shear stress, approximating small

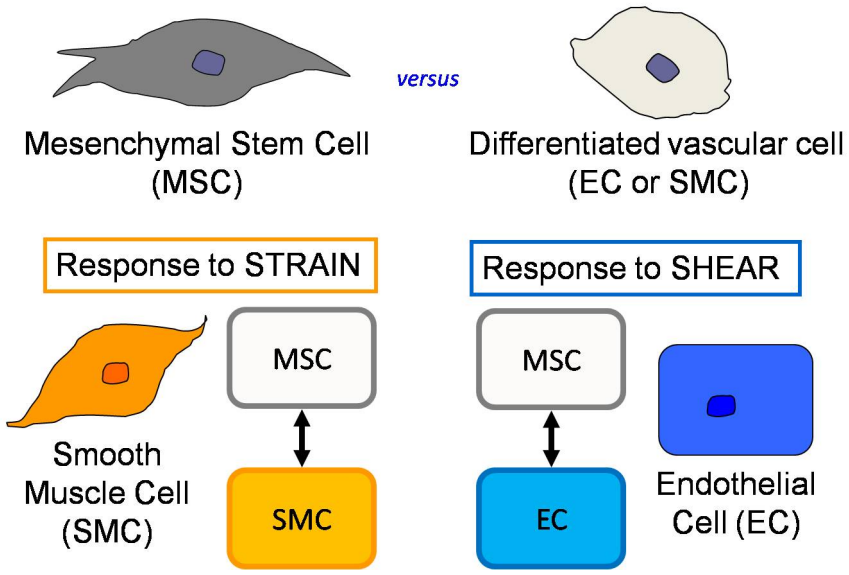


Figure 1: Overview of cell and force type comparisons included in dissertation. The response to equibiaxial cyclic strain of MSCs and SMCs is compared in Aim 1 (left). In Aim 2, MSCs and ECs are compared using their response to steady laminar shear stress (right). Aim 3 employs high-throughput assessments for both cell type comparisons to better characterize the signaling responses to cyclic strain or shear stress.

and large vessel shear stress levels, respectively. Shear-responsive gene expression was quantified for a panel of eight immune and inflammatory markers, including those also used to infer endothelial differentiation. Correlation of gene and protein expression for Pecam1, VE-Cad, and vWF was determined using immunocytochemistry and confocal imaging. Cell number quantification and effect of underlying protein substrate were used to further understand how MSCss respond to applied shear stress. Results are described in Chapter 5.

1.3.3 Specific Aim 3.

Determine the gene expression signaling profile, using cDNA microarrays, for MSCs exposed to cyclic strain or shear stress and vascular differentiated cells exposed to the same force. The *working hypothesis* is that the signaling profile of gene and protein expression is conserved between MSCs and terminally differentiated cells in response to site-appropriate forces characteristic of the originating vascular tissue. A high-throughput strain and high-throughput shear analysis were completed, comparing MSCs and SMCs

in the former and MSCs and ECs in the latter after exposure to the physical forces described above. Microarray analysis was first completed using traditional methods, identifying mechanoresponsive genes with significance and fold change criteria and predicting functional relevance with bioinformatics software. These results are described separately for the strain comparison (Chapter 4) and shear comparison (Chapter 6). Preliminary analysis of whole genome mechanoresponse modeling, comparing across both cell type and force condition, is included in Appendix E.

1.4 Additional materials

Context for the primary research described above is provided in additional chapters. A review of relevant work completed by others is included in Chapter 2. Chapter 7 discusses the overall implications of work completed to address these specific aims. Appendices include detailed protocols and peripherally-related studies completed to understand MSCs biology.

1.5 Clarification of terms

Throughout this thesis, two terms are used repeatedly to describe mechanosignaling responses: 'significant' and 'conserved.'

- For this document, the term 'significant' indicates a statistical difference between two populations. Two-factor ANOVA and paired t-tests are the most frequently used statistical tests to assess differences. Unless otherwise specified, differences are considered significant when the probability of occurrence by chance is less than 5% (e.g., $p < 0.05$). Biological significance of these changes is suggested, but not proven, by this mathematical definition.

- The term 'conserved' describes quantities 'maintained constant during a process of chemical, physical, or evolutionary change' [184]. In biology-related fields, conserved signaling molecules often refer to presence of a gene or protein in different species, based on homology between gene or protein sequences or, more recently, network motifs [50]. This dissertation proposes mechanoresponsiveness as an additional

property by which to define 'conserved' elements. Conserved mechanoresponsive molecules referenced in this document alter by at least 1.5-fold magnitude, the detection threshold of gene assessment methods used, and are statistically significant ($p < 0.05$, n=3) according to at least three measures: paired t-tests in both cell types (MSCs and SMCs or MSCs and ECs) and corrected force-dependent p-value from two-factor ANOVA. Molecules can be conserved in terms of strain response between MSCs and SMCs (Chapters 3 and 4) or shear stress response between MSCs and ECs. A few molecules were identified with conserved force-responsiveness in all conditions (similar changes across three cell types and two force types), as listed in Appendix E.

1.6 Significance of Results

Results from this dissertation contribute to the fields of cardiovascular biology, stem cells, tissue engineering and regenerative medicine, and mechanobiology. New instances of gene mechanosensitivity were identified in multiple cell types and due to both cyclic strain and shear stress. This data provides one of the first descriptions of MSCs signaling in response to vascular-relevant mechanical cues, distinct from differentiation-focused studies or those using orthopedic levels of physical forces. MSCs responded to applied forces through a combination of changes also present in differentiated vascular cells and those observed only in MSCs. Differences in MSCs and vascular cell signaling necessitate further scrutiny before these cells can be confidently used in a vascular cell-based therapy. The systematic comparisons and high-throughput data analysis used here to understand mechanoresponse may also be applied to other cell types. In addition, the theme of mechanoresponse as a combination of conserved and unique features provides a framework to use in searching for fundamental rules governing the mechanical-chemical interface.

CHAPTER II

BACKGROUND AND SIGNIFICANCE

2.1 Overview

This work builds on previous studies establishing the importance of mechanosignaling for vascular physiology, as well as evidence indicating MSCs may improve vascular function. The following literature review focuses on the biology of MSCs, mechanical cues in the vasculature, and mechanoresponses of smooth muscle cells and endothelial cells. Current knowledge regarding mechanosensitivity of MSCs is also presented.

2.2 Review of Relevant Literature

2.2.1 Mesenchymal stem cell isolation and characterization

Human mesenchymal stem cells (MSCs) are derived from the bone marrow and isolated using a density gradient separation and subsequent plating of the mononuclear cell fraction. MSCs are 0.001-0.01% of the resulting adherent cells [225]. MSCs have historically been defined according to: (a) a protein expression profile (Figure 2); (b) the potential to differentiate along osteogenic, chondrogenic, and adipogenic lineages; and (c) an adherent, spindle-shaped morphology [225, 65]. Since neither the protein markers nor differentiation capacity are unique to MSCs, one outstanding challenge in the field is the lack of a conclusive assay to define MSCs. Furthermore, variations in tissue source, isolation method, and characterization of cells have resulted in ambiguities throughout the literature regarding the equivalence of cells used by different groups [302]. For experiments completed for this dissertation, the term MSCs refers to cells commercially available through Lonza that have been harvested and cultured from normal human bone marrow and characterized for surface marker expression (CD105+, CD166+, CD29+, CD44+, CD14-, CD34-, and CD34-) and potential to differentiate along adipogenic, chondrogenic, and osteogenic lineages [165]. Verification of surface protein marker expression and differentiation potential

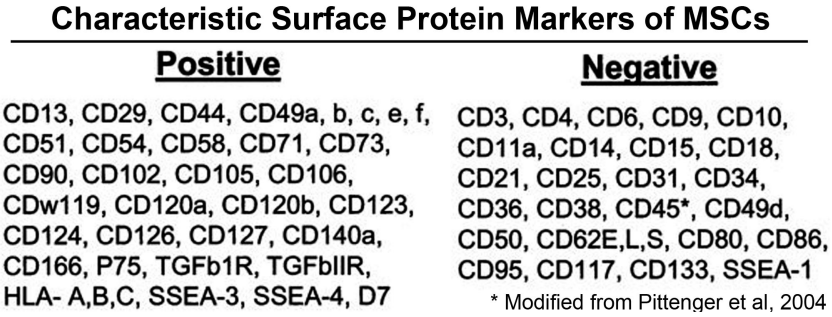


Figure 2: Characteristic Protein Surface Marker Expression in Mesenchymal Stem Cells. Human adult bone marrow-derived MSCs are characterized by orthopedic-related differentiation potential, adherent and spindle-shaped morphology, and positive or negative expression of a panel of surface proteins (listed above). Protein list modified from [226].

was repeated for donors used in this dissertation with MSCs expanded to experimental use passage (Appendix A).

2.2.2 Contributions of mesenchymal stem cells in vascular therapies

MSCs are an attractive option for cardiovascular cell-based therapies due to their proliferative, multilineage, and paracrine potential [122, 179, 224, 30]. Mesenchymal stem cells have been proposed as a multipotent, adult stem cell source for use in cardiovascular applications [226, 80, 87]. Rapid growth in the number of recently published articles related to mesenchymal stem cells highlights the growing interest of the scientific community in MSCs-based therapies, and specifically for vascular-related applications (Figure 3). Several studies suggest beneficial effects of MSCs may be due to differentiation into smooth muscle-like [147, 204, 62, 168, 167, 86, 6, 9, 316] or endothelial-like [45, 118, 37, 329, 315, 214] cells. However, recent work suggests the source of beneficial effects of MSCs on host tissue can occur through paracrine effects [54, 133, 207, 230]. The specific contribution of MSCs to vascular repair or regeneration may be a combination of both these mechanisms.

2.2.3 Importance of mechanical cues in the vasculature

Mechanical forces in the vasculature (Figure 4) have been well studied in large blood vessels such as the aorta and pulmonary artery [10, 154]. Heart contractions and the radial

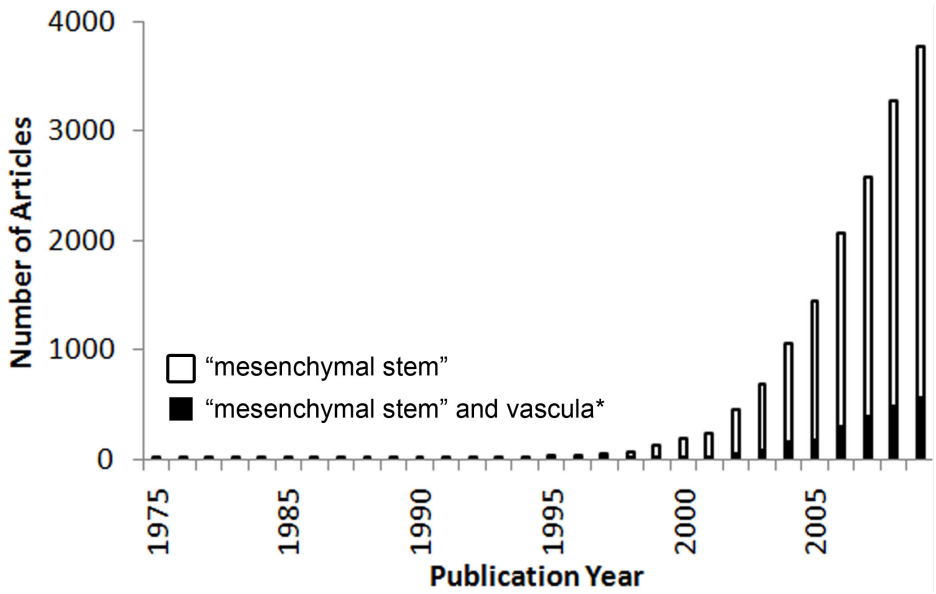


Figure 3: Publications related to MSCs. Annual manuscript publications related to MSCs in general or to MSCs and the vasculature. Data based on ISI Web of Knowledge database searches for either "mesenchymal stem" (outlined bars) or "mesenchymal stem" and vascula* (solid bars) [236]. In 2009, 562 of a total of 3205 "mesenchymal stem" publications related to the vasculature.

compliance of vessels result in a pulsatile blood pressure profile and cyclic distension. The tunica media, the thickest layer of the vessel wall and populated primarily with SMCs, is expected to sustain a significant portion of the cyclic strain in both the radial and circumferential directions. Strain mediates changes in SMCs that may affect cytoskeleton contraction and, subsequently, vessel compliance and downstream blood pressure. Blood flow through the vessel lumen induces shear stress on the inner surface, lined with an endothelial cell monolayer. Steady laminar shear stress on endothelial cells is important to maintain a quiescent, non-inflammatory, and non-immunogenic state, pivotal in preventing blood clotting and subsequent closure of the vessel.

2.2.4 Overview of mechanobiology

Mechanobiology is the study of cells biological response to mechanical loads and the signaling pathways by which these loads are transduced into a cascade of cellular and molecular events [305]. Known mechanisms, measurement methods, and models of cellular

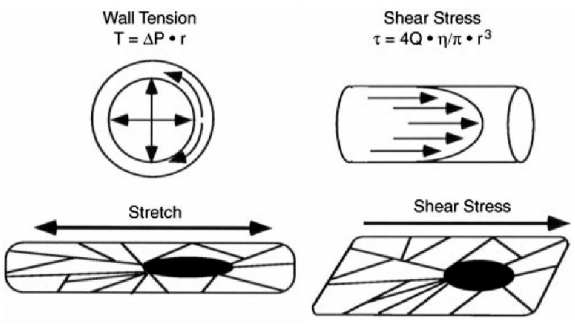


Figure 4: Physical forces in the vasculature. Adapted from [10]. Cyclic strain acts on all layers of the vessel wall, including ECs and SMCs, while fluid shear stress acts on the ECs lining the vessel lumen.

reaction to applied physical forces have been recently reviewed [99, 117]. During development, mechanical cues are essential in formation of several regions including limbs [202], lungs [112], and the aortic arch [322]. Throughout adult life, mechanical cues are critical for normal function in many tissues, including the ear [77], eye [277], bone [244], cartilage [32], and heart [151]. Mechanosensing can occur via adhesive connections and associated cytoskeletal networks or via the cell membrane and membrane-associated proteins [17, 108, 297, 331]. These physical cues are expected to trigger conformational changes of signaling molecules that activate cell signaling pathways [296]. Cells unable to translate environmental mechanical cues into biochemical action via gene and protein signaling pathways can trigger disease [111, 211]. Cell signaling responses triggered by applied physical forces depend not only on the affected cell and tissue type [27, 95], but also on specific force parameters such as magnitude and duration [288]. Several groups have investigated the role of specific signaling components in response to applied physical force. The following sections describe these results in terms of the cell types and forces relevant to this dissertation.

2.2.5 Signaling response of vascular smooth muscle cells to cyclic strain

Adult smooth muscle cells respond to cyclic strain with an increase in proliferation, increased collagen production, changes in cytoskeletal composition and arrangement, and altered gene and protein expression. Mechanical tension is also present at sites of smooth muscle myogenesis [115] and has been shown in vitro to upregulate expression of genes

related to differentiation of SMCs [170, 328], suggesting mechanical tension contributes to development of SMCs. Mechanical strain mechanosensors, downstream genes and proteins targets, and subsequent functional effects in SMCs were reviewed by Haga et al [88]. In brief, the few studies investigating the effects of strain on human SMCs have focused primarily on changes in gene expression [73, 249, 195], with one study assessing changes in proteoglycan synthesis and organization [153]. Strain-induced changes, particularly in terms of membrane or cytoskeletal proteins, have been extensively studied in rat smooth muscle cells [26, 235, 161, 265, 190]. Strain was found to alter focal adhesion-related components, inducing vinculin expression and transient paxillin expression within minutes [52]. Exposure to strain for hours can alter cytoskeletal protein expression by upregulating the SM1 isoform of smooth muscle myosin heavy chain [235]. Furthermore, two days of strain appears to shift the functional status of SMCs from contractile to synthetic, reducing expression of alpha-smooth muscle actin and calponin contractile proteins and increasing expression of vimentin, an intermediate filament protein [26].

Interleukin 8 (Il8), also known as CXCL8, is a secreted chemokine involved in inflammation, angiogenesis [16], and neutrophil chemoattraction. IL8 protein binds to receptors IL8R-alpha (CXCR1) and IL8R-beta (CXCR2). Il8 signaling affects inflammation-related vascular disorders including atherogenesis and hypertension [22, 131]. Multiple studies have shown that cyclic strain increases Il8 gene and protein expression in airway epithelial and smooth muscle cells [295, 216, 145], endothelial cells [209], endometrial stromal cells [90], and uterine smooth muscle cells [166]. In contrast, cyclic strain of skeletal myotubes results in decreased IL8 protein secretion in skeletal myotubes [287]. Il8 expression is also induced by shear stress, as detected in human umbilical cord ECs [42]. No studies to date have evaluated mechanosignaling of Il8 in vascular smooth muscle cells. Results generated for this dissertation thus fill a gap in the literature, demonstrating novel mechanosensitivity of this functionally important molecule in another vascular cell type.

2.2.6 Signaling response of endothelial cells to steady laminar shear stress

The response of ECs to applied shear stress depends on both the vessel bed used for harvest of ECs [27, 43, 63, 276] and the type of shear applied, such as oscillatory, pulsatile, or steady laminar [41, 101]. Steady laminar shear stress promotes atheroprotective, anti-inflammatory conditions associated with functional endothelium [309]. Conversely, atherosclerosis occurs most commonly in regions of oscillatory, turbulent, and/or low shear stress [280, 234]. This dissertation focuses on shear effects observed on human aortic ECs under steady laminar shear stress, similar to the physiologic shear stress profile present in large vessels [313]. Laminar shear stress on ECs affects cell functions including: cell survival, proliferation, lipid metabolism, cytoskeletal organization, ECs turnover and macromolecular permeability [44], migration [268], leukocyte adhesion [187, 286, 330], and numerous changes in gene and protein activation [44, 23, 36, 314]. Immune response and inflammation are two key functions related to cardiovascular health and influenced by shear of the endothelial layer [97]. Genes in these functions with an established laminar shear-response in aortic ECs include: cyclooxygenase 2 (Cox2) [101, 97], endothelial nitric oxide synthase (eNos) [177, 291], heme oxygenase 1 (Hmox1) [101, 308], Kruppel-like factor 2 (Klf2) [109, 61], monocyte chemotactic protein 1 (Mcp1) [41, 259, 260], platelet-endothelial cell adhesion molecule (Pecam1) [212, 290], vascular endothelial cadherin (VE-Cad) [141, 201].

Applied shear stress has been shown to promote differentiation along an endothelial lineage in multiple stem cell types, including endothelial progenitor cells (EPC) [], embryonic stem cells (ESC) [], and MSCs []. Gene and protein indicators used to track endothelial-like differentiation include Pecam1, VE-Cad, and vWF [239]. Both Pecam1 and VE-Cad are shear-responsive in ECs and increased in stem cells exposed to shear stress []. Collectively, Pecam1 signaling is both a marker of differentiation and shear stress response characteristic of ECs. Activation of Pecam1 signaling

2.2.7 Signaling response of mesenchymal stem cells to cyclic strain

Several bioreactor systems have been designed for application of strain to MSCs: uni- and equi-axial strains on MSCs monolayers [178, 264] and uniaxial and more complex strains on 3-D cell-seeded scaffolds [4]. Applied strain systems have been employed to differentiate MSCs along osteogenic [258, 113, 139, 56, 76], chondrogenic [76, 105, 106, 160, 28], and tendon and ligament [223, 299, 256, 124] lineages. Several groups report the ERK1/2 and p38 MAP kinase pathways are cyclic strain-responsive in MSCs [261, 237], with one group also reporting strain-induction of BMP2 [273]. For heart valve applications, strain of MSCs in monolayer results in collagen synthesis similar to that observed in aortic valve interstitial cells when strained under the same conditions [144]. The Li laboratory (UC-Berkeley) has investigated MSCs for vascular therapies and demonstrated a differential response to uniaxial versus equibiaxial cyclic strain. They and others have shown that uniaxial strain upregulates expression of SMCs-related differentiation genes and proteins [218, 148, 146, 162, 137].

2.2.8 Signaling response of MSCs to fluid shear stress

MSCs have been exposed to a range of shear stresses in vitro [327, 245, 100, 55, 232]. Several studies focus on fluid shear stress as a means to differentiate MSCs along osteogenic [245, 232, 143] or chondrogenic [299, 250] lineages. ERK1/2 [132], MAP kinase and calcium [238], as well as NF-kappa-B [130] and nuclear factor of activated T cells (NFAT) [7], have been implicated in the response of MSCs to applied fluid shear. Shear stress magnitudes relevant to the skeletal tissues, with which MSCs are frequently associated, are typically several orders of magnitude lower than that relevant for large diameter blood vessels. Furthermore, applied force stimulation for the purpose of MSCs differentiation typically occurs over days to weeks, a timescale that does not capture the initial mechanosignaling events that are the focus of this dissertation. Fluid shear of MSCs also upregulates gene expression of the inflammatory marker cyclooxygenase 2 (Cox2) [7], as is also observed in ECs.

For cardiovascular regenerative medicine applications, physiologic responses to mechanical cues may be a determining factor in the success of cell-based therapies. This dissertation compares mechano-related signaling of MSCs and normal endothelial and smooth muscle cells to cardiovascular-relevant physiologic forces. Results from this work help uncover which signaling pathways will respond similarly in MSCs versus those that will signal in atypical ways. Once these molecules are identified, future studies are needed to determine the benefit or harm of differential signaling.

CHAPTER III

CONSERVED AND CELL TYPE-DEPENDENT SIGNAL TRANSDUCTION IN MESENCHYMAL STEM CELLS AND SMOOTH MUSCLE CELLS EXPOSED TO MECHANICAL STRAIN

3.1 Abstract

Mechanical cues cause changes in cell signaling. In the context of stem cell therapies, these changes may affect therapy efficacy. Mesenchymal stem cells (MSCs) are proposed for use in vascular therapies, yet little is known about their signaling in response to cyclic strain, a typical vascular mechanical cue. We compared MSCs and aortic smooth muscle cell (SMCs) for signal transduction gene expression under standard growth conditions and in response to applied strain (10%, 1 Hz). MSCs and SMCs cultured in respective growth media express significantly ($p \leq 0.05$, n=3) different levels of 42 of 84 signal transduction genes assessed, suggesting MSCs will respond differently than SMCs if introduced as a vascular therapy. When exposed to applied cyclic strain, SMCs responded within 24 hours with increased number and magnitude change gene expression relative to MSCs. Il8, Vcam1, and Hmox1 were strain-responsive in both cell types, with similar magnitude fold-changes between cell types in spite of 100-fold differences in relative expression levels. Il8, Vcam1, and Hmox1 are all involved in inflammatory-related signaling. Our results suggest that cells respond to applied mechanical force using a combination of conserved and cell-type specific mechanisms.

3.2 Background

Mechanosignaling of stem cells compared with differentiated cells is poorly understood. Mechanical cues trigger changes in cell signaling observable at the nucleotide, transcription, translation, post-translation and second messenger levels [111, 221, 305]. Previous studies of the cellular effects of mechanical cues focus primarily on mechanoresponses

of differentiated cell types or tissues [292, 111]. Current efforts to develop vascular cell-based therapies require broadening this focus to include the mechanoresponses of stem and progenitor cells. This manuscript focuses on how mesenchymal stem cells, a putative cell source, respond to vascular-relevant levels of applied cyclic strain.

Vascular smooth muscle cells experience and respond dynamically to cyclic strain. In the vascular system, smooth muscle cells (SMCs) experience cyclic strain due to pulsatile heart contractions. Cyclic strain affects vascular smooth muscle cell functions including alignment, migration, proliferation, and differentiation [157, 251, 233]. Signaling pathways mediating the SMCs strain-response are activated within minutes (e.g., MAPK family and PKC) [157, 233], hours (e.g., Notch3 and Hedgehog) [191], and days (e.g., smooth muscle contractile and osteoblast characteristic genes) [19, 200] of applied cyclic strain. Pathological conditions such as hypertension or atherosclerosis can alter vessel mechanical properties and associated mechanosignaling [152]. Several groups, including ours, have attempted to engineer vascular smooth muscle-based 3-D constructs for in vitro study of vascular biology and to create a vascular substitute [269, 156, 199]. Due to the shortage of available SMCs and their limited regenerative capacity, clinically-relevant vascular therapies will likely require an alternate cell source.

Potent trophic effects make mesenchymal stem cells (MSCs) an attractive choice for a vascular therapy [230, 225]. MSCs are derived from adult bone marrow and characterized by isolation method and a panel of cell surface protein markers [226]. These multipotent stem cells self-renew and have the potential to differentiate along osteogenic, chondrogenic, and adipogenic lineages. MSC-like cells, including SMCs and pericytes, surround endothelial cells throughout the vasculature [182, 51]. In some cases, MSCs adopt SMC-like traits including expression of genes and proteins involved in smooth muscle contraction [134, 149]. MSCs secrete angiogenic factors, remodel the extracellular matrix in a wound environment, and modulate the immune and inflammatory responses [247, 194, 317, 133]. Current clinical trials are testing safety and efficacy of MSCs for treating ischemic stroke, acute myocardial infarction, congestive heart failure, and cardiac surgery [197, 80, 122]. Studies of MSCs mechanoresponse to date have focused

on differentiation of MSCs along SMC-like or orthopedic lineages under site-appropriate mechanical force regimes [218, 104, 148, 243, 273]. Activation of more general signaling pathways in MSCs exposed to applied mechanical forces, in particular vascular-relevant conditions, is unknown.

In this chapter, signal transduction gene expression is compared between human adult bone marrow-derived MSCs and human aortic SMCs (Figure 5). Initial signaling conditions were compared by gene expression in MSCs and SMCs cultured in standard growth media. To compare mechanoresponses, signal transduction gene expression were compared in MSCs and SMCs exposed to a range of matched equibiaxial cyclic strain conditions. We find the signal transduction response to strain includes conserved and cell-type specific elements.

3.3 Results

3.3.1 Signal transduction genes robustly expressed

MSCs and SMCs cultured under maintenance conditions have similar distributions of genes detected during 40 cycles of qRT-PCR, as highlighted by the cumulative distribution lines in Figure 6. Housekeeping genes Actb, Gapdh, and Rpl13a are among the earliest detected in both cell types, with all 5 housekeeping genes detected by threshold cycle 25 (Supplemental Figure 12). Most signal transduction genes assessed are detected between threshold cycles 20.00 and 30.00. By threshold cycle 25.00, 42% and 44% genes are detected in MSCs and SMCs, respectively; by cycle 30, 71% and 76% genes are detected in MSCs and SMCs. When cultured under cell type-specific maintenance conditions, SMCs have a moderate (1.25-fold), but significant ($p \leq 0.05$, n=3), increase in the average overall expression level of signal transduction genes relative to MSCs (SMCs-C_t=26.66$\pm$0.15 vs. MSCs-C_t=26.98$\pm$0.06). Genes with highest relative expression in both cell types affect the cell cycle (Cdkn1a), extracellular matrix (Fn1), signaling regulation through growth factors (Igfbp3) and transcription (Hsbp1).

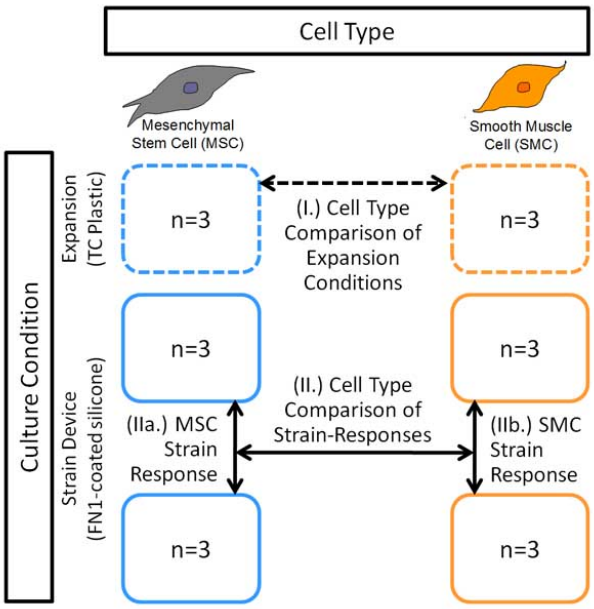
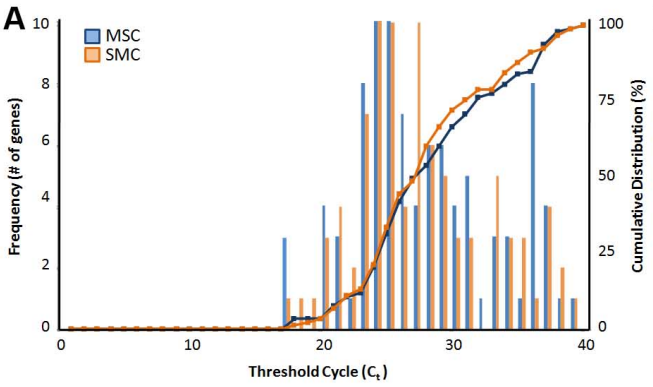


Figure 5: Experimental groups compared for expression of signal transduction genes, assessed using PCR arrays. (Comparison I.) Gene expression levels initially present in MSCs and SMCs were compared under expansion conditions in standard maintenance culture medium (MSCsGM or SmGM2, respectively). (Comparison II.) Strain responses for both cell types were subsequently compared using the differential responses of strain versus static samples for MSCs (IIa.) and SMCs (IIb.)



B

Threshold Cycle Range	Genes Detected in MSC &SMC
<16	---
16-20	ACTB, FN1, GAPDH, RPL13A
20-25	ATF2, BAX, BIRC2, CCL2, CCND1, CDKN1A, CEBPB, FAS, FASN, GYS1, HPRT1, HSF1, IGFBP3, JUN, MDM2, NFKB1, NRIP1, ODC1, PRKCA, TFRC, TP53, VEGFA
25-30	BCL2A1, BCL2L1, BMP4, BRCA1, CDK2, CDKN1B, FOS, HK2, HSP90AA2, ICAM1, IKBKB, IRF1, MYC, NAIP, PPARG, PRKCE, PTCH1, SELPLG, TMEPAI
30-35	BIRC3, CCL20, CYP19A1, GREB1, LEF1, PECAM1, TANK, TCF7
35-40	CD5, CSF2, LTA, NOS2A, TNF
Not Detected	---

Figure 6: Signal transduction gene expression levels in MSCs and SMCs under maintenance culture conditions. (A) Histogram (bars) and cumulative distribution (overlaid lines) of average threshold cycle raw values for all wells assessed on a signal transduction PCR array, showing similar profiles for MSCs (blue) and SMCs (orange). Triplicate arrays per group. (B) Table of signal transduction genes detected in both cell types for a given threshold cycle range.

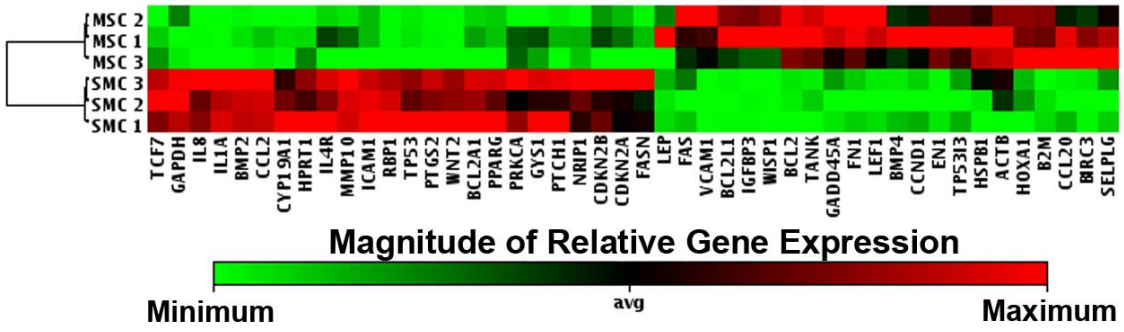


Figure 7: Heatmap of relative expression values (2-$\triangle C_t$) for genes with significantly ($p \leq 0.05$, n=3) different expression in MSCs and SMCs cultured under maintenance conditions. Two-dimensional clustering groups samples (arrays) with similar overall expression horizontally and individual genes with similar expression levels vertically.

3.3.2 MSCs and SMCs differ in baseline expression of specific signal transduction genes

Four of five housekeeping genes are expressed significantly ($p \leq 0.05$, n=3) differently in SMCs versus MSCs: B2m (2.47-fold up in SMCs), Actb (1.3-fold up), Gapdh (1.5-fold down), and Hprt1 (2.1-fold down). Rpl13a expression does not significantly (p=0.932, n=3) differ between MSCs and SMCs. In terms of signal transduction genes, 42 of 84 genes assessed differ significantly between MSCs and SMCs, determined using an unpaired t-test. Similar numbers of genes are expressed at relatively higher levels (24 genes more highly expressed in SMCs; 22 genes in MSCs). Genes with comparatively highest expression in SMCs include Wnt2 (133-fold), Il8 (126-fold), and Rbp1 (104-fold) and in MSCs include Vcam1 (49-fold), Wisp1 (23-fold), and En1 (11-fold).

3.3.3 Morphology of samples exposed to equibiaxial strain indistinguishable from static controls

MSCs (Figure 8A-B) and SMCs (Figure 8D-E) exposed to applied strain for 24 hours are not visibly different from parallel static controls in terms of cell size, shape, or multicellular arrangement, as assessed using phase microscopy. Phase images of samples subjected to applied strain or parallel static culture for 6 or 24 hours show an increase in cell density in all groups (MSCs-Static, MSCs-Strain, SMCs-Static, and SMCs-Strain; data not shown).

3.3.4 Comparison of overall signal transduction gene expression in strain model system

Average threshold cycle (C_t), an indicator of overall gene expression level, is significantly ($p < 0.0001$, n=6) dependent on cell type, based on two-way ANOVA. MSCs have approximately 2-fold lower overall signal transduction gene expression than SMCs (SMCs-C_t=27.14$\pm$0.39 vs. MSCs-C_t= 28.24$\pm$0.22) when cultured on fibronectin-coated silicone. Paired t-test comparison of average threshold cycles within a single cell type indicated gene expression levels are significantly different under strain and static conditions for MSCs ($p \leq 0.01$, n=3; 1.3-fold increase in strain samples) (Figure 8C), but not SMCs (p=0.636, n=3) (Figure 8D). Variation in overall average threshold cycle within a group (n=3 arrays) was consistently 2-fold greater for SMCs than MSCs for all culture condition comparisons (maintenance, static culture on fibronectin-coated silicone, and applied strain on fibronectin-coated silicone), although this difference was not significant (p=0.11, n=3).

3.3.5 Strain responses of SMCs and MSCs

We defined 'strain-responsive' genes as those with significant ($p \leq 0.05$, n=3) differences in expression levels between strain vs. static samples of at least 1.5-fold up- or down-regulation. More strain-responsive signal transduction genes were identified in SMCs than MSCs (9 versus 5, from a group of 84 genes assessed) (Figure 9A). Two genes, Interleukin 8 (Il8) and Vascular Cell Adhesion Molecule 1 (Vcam1), were strain responsive in both cell types. Il8 increases in response to strain (MSCs: 2.24$\pm$0.35; SMCs: 2.59$\pm$0.31). In the strain model system, average Il8 expression levels are 160-fold greater in SMCs compared to MSCs (Figure 9B). VCAM1 decreases in response to strain (MSCs: -1.61$\pm$0.04; SMCs: -4.35$\pm$0.07). Average Vcam1 expression is 127-fold greater in MSCs than SMCs (Figure 9C). Bone morphogenetic protein 4 (Bmp4: -1.54$\pm$0.06 fold change), Homeobox A1 (Hoxa1: -1.56$\pm$0.09), and P-selectin ligand (Selplg: +1.58$\pm$0.20) are strain-responsive in MSCs, but not SMCs. CCAAT/enhancer binding protein beta (Cebpb: +1.97$\pm$0.53), Fatty

Acid Synthase (Fasn: +1.52±0.22), Interleukin 1 alpha (Il1α: +1.47±0.11), Interferon regulatory factor 1 (Irf1: 1.47±0.16), Matrix metallopeptidase 7 (Mmp7: -1.85±0.03), Cellular retinol binding protein 1 (Rrp1: -1.67±0.03), and CD71/Transferrin Receptor C (Tfrc: +1.58±0.15) are strain-responsive in SMCs, but not MSCs.

A less stringent definition of 'strain-responsive', generated by removing the minimum fold change criteria and reducing the significance criteria ($p \leq 0.10$, n=3), identifies approximately 5 times as many additional strain-responsive genes in SMCs as MSCs (SMCs: 5 and 9 additional genes for respective criteria changes vs. MSCs: 0 and 3 genes) (Figure 9A). These less stringent 'strain-responsive' criteria identify three additional genes as having conserved strain responsiveness across cell type: Baculoviral IAP repeat-containing 2 (Birc2), Bmp4 (identified using high stringent criteria only in MSCs), and Il1α (identified using high stringent criteria only in SMCs). For both high stringency (p≤0.05 and $|FC| \geq 1.5$) and low stringency (p≤0.10 only) strain-responsive criteria, MSCs have a reduced number and magnitude fold-change of strain-responsive genes than SMCs (Table 1). In addition, comparison of strain-responses with initial expression levels under maintenance culture shows that strain-responsive gene expression is independent of initial values (Supplemental Figure 13).

3.3.6 Gene expression dependence on applied force and cell type

Two-factor ANOVA was used to determine the dependence of gene expression on force condition, cell type, or an interaction between factors. Results of ANOVA are summarized in Figure 10, with complete results for each gene listed in Table 1. Approximately seven times as many genes have expression significantly ($p \leq 0.05$, n=3) dependent on cell type as force condition (48 vs. 7 genes) (Figure 10A). Statistical analyses by t-test and ANOVA were combined to generate lists of genes with expression affected by cell type (Supplemental Table 4) or mechanical strain (Supplemental Table 5).

Two-factor ANOVA corroborated differences in cell type expression profiles identified in the maintenance culture comparison. 4 of 4 housekeeping genes and 27 of 42 signal transduction genes differ between cell types significantly ($p \leq 0.05$, n=3) when cultured

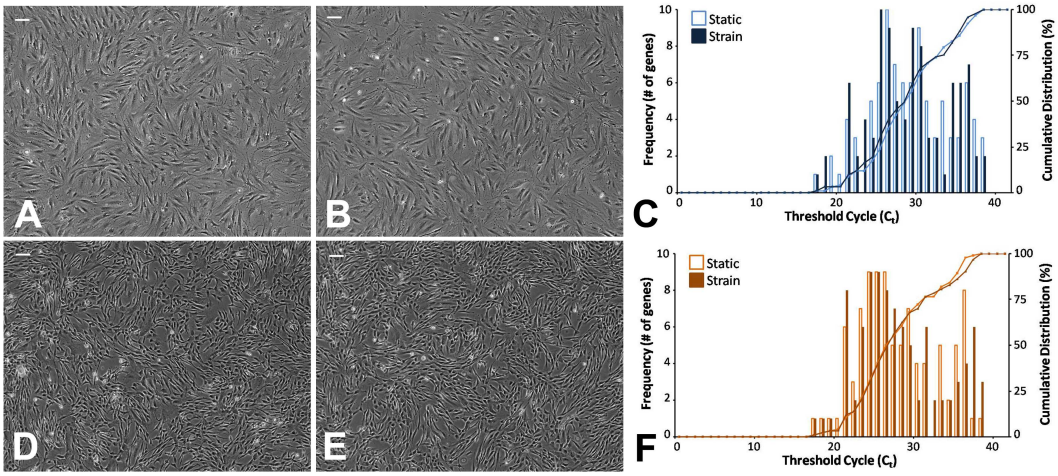


Figure 8: Morphology and signal transduction gene expression levels of MSCs and SMCs exposed to equibiaxial strain (10%, 1 Hz) or static culture for 24 hours. Neither MSCs (A-B) nor SMCs (D-E) show observable differences in cellular patterning after applied strain (B, E) compared with parallel static controls (A, D), as assessed using phase microscopy. Overall expression levels of signal transduction genes are similar under strain (solid bars) and static (outline bars) culture conditions for both MSCs (C) and SMCs (F). Scale bars = 100 μm.

on either TCPS or the strain model system (Table 4). Five genes showed significant cell type- or interaction-dependent expression only when cultured in the strain model system, in contrast to 15 genes with differences in cell type unique to the maintenance culture environment (Table 4).

Most genes identified via ANOVA with significant ($p \leq 0.05$, n=3) force-dependent expression (Figure 10B) had been identified as strain-responsive using criteria outlined above (Vcam1, Il8, Rbp1, Tfrc, Bmp4, and Fn1) (Figure 9A) and also showed significant cell type-dependent gene expression. Of these genes, Vcam1 and Tfrc expression was significantly (p=0.021 and p=0.037, respectively; n=3) dependent on an interaction between cell type and force condition. SMCs samples had greater magnitude fold change response to strain of Vcam1 and Tfrc than MSCs samples. Mdm2 p53 binding protein homolog (Mdm2) expression was dependent significantly on force condition (p=0.041, n=3), but not cell type (p=0.296, n=3) nor interaction (p=0.828, n=3). Mdm2 was identified as force-responsive via two-factor ANOVA, but not t-test comparisons, due to the increase in effective sample size from pooling samples from both cell types (ANOVA static vs. strain: n=6 versus t-tests:

n=3). Although Mdm2 expression was not significant in paired t-tests (MSCs: p=0.112; SMCs: p=0.296), expression did increase in all samples in response to strain (MSCs: 1.22±0.15; SMCs: 1.28±0.20) (Table 2).

Table 1: Table showing distribution of up- and down-regulated genes.

			Mesenchymal Stem Cells		Smooth Muscle Cells	
		Fold Change (Strain/Static)	↑	↓	↑	↓
Strain-Responsiveness Criteria	High Stringency (p≤0.05, |FC|≥1.5)	# genes	2	2	6	3
		Range FC	*-1.56 - 2.24*		*-4.35 - 2.59*	
	Low Stringency (p≤0.10; no FC threshold)	# genes	2	1	13	1
		Range FC	*-1.43 - 1.4*		*-1.75 - 2.3*	
	Total (High + Low)	# genes	4	3	19	4
		Range FC	*-1.56 - 2.24*		*-4.35 - 2.59*	

3.3.7 PCR array sensitivity limits analysis of genes with low expression levels

Analysis of some signal transduction genes was limited by incomplete data sets. Expression of 9 of 84 signal transduction genes (but no housekeeping or control wells) assessed using this array could not be detected on at least half the arrays. Genes with a 'not detected' value on at least 9 of 18 PCR arrays include, in order of highest to lowest undetected rate: Il4 (16/18 arrays), Il2 (15/18), Sele (14/18), Cxcl9 (13/18), Tert (12/18), Faslg (12/18), Foxa2 (9/18), and Klk2 (9/18). These undetected readings correlate with genes whose expression ranks in the lowest 10% on a given array for both MSCs (r=0.754) and SMCs (r=0.768), suggesting the 'not detected' readings reflect low or absent gene expression rather than technical errors in data acquisition. Most 'not detected' errors were distributed evenly across MSCs and SMCs samples and static, strain and maintenance culture groups. However, FOXA2 'not detected' expression errors occurred consistently and exclusively in MSCs samples.

3.3.8 Temporal Kinetics of Gene Expression Changes

To quantify the Il8 and Vcam1 strain-response during the first 24 hours of applied strain, mRNA expression level fold changes (strain/static) were determined via standard qPCR using samples exposed to applied strain or parallel static culture for 0, 2, 6, 12, or 24 hours

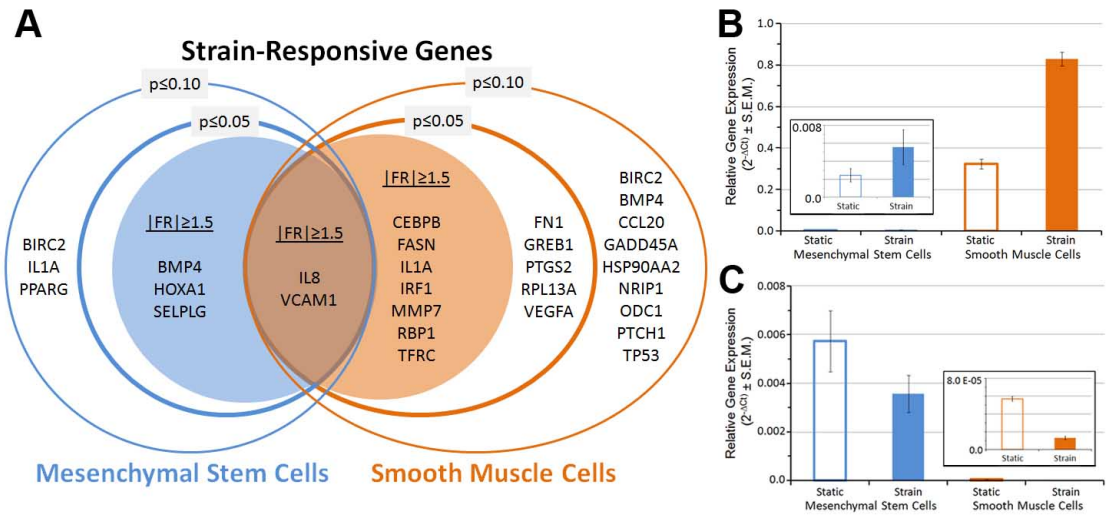


Figure 9: Gene expression changes in MSCs (blue) and SMCs (orange) in response to applied cyclic strain (10%, 1 Hz for 24 hr) assessed using a signal transduction PCR array. (A) Venn diagram comparing genes identified in either MSCs or SMCs whose expression differs moderately significantly ($p \leq 0.10$, thin outer boundary) or highly significantly ($p \leq 0.05$, thick inner boundary) in response to strain. Shaded regions indicate fold up- or down-regulation ≥ 1.5 for highly significantly strain-responsive genes. Interleukin 8 (Il8) and Vascular Cell Adhesion Molecule-1 (Vcam1) expression is highly significantly ($p \leq 0.05$) altered ($|FC| \geq 1.5$) in both cell types. (B) Relative gene expression of Il8 in MSCs and SMCs under static (outlined bar) or strain (solid bar) culture conditions. (C) Relative gene expression of Vcam1.

(n=3-4/group) (Figure 11). Kinetic analysis of Il8 and Vcam1 confirmed their up- and down-regulation, respectively, after 24 hours applied cyclic strain. In SMCs, Il8 is significantly ($p \leq 0.05$, $n \geq 3$) upregulated after 12 hours (1.79 ± 0.27-fold) and 24 hours (2.91 ± 1.92) applied strain. In MSCs, Il8 upregulation is significant only after 24 hours applied strain (1.88 ± 0.52-fold).

The bioinformatics software Ingenuity Pathways Analysis (IPA) was used to determine connections between strain-responsive signaling molecules. The primary signaling network identified from this analysis is associated with 'cardiovascular system development and function,' suggesting the general signal transduction genes identified as strain-responsive using PCR arrays are also important for the cardiovascular system. Il8 has been shown to upregulate Vcam1 in other studies. Additional potentially strain-responsive molecules were identified via IPA. Interleukin 8 indirectly regulates Vascular cell adhesion molecule 1. Other molecules also regulating Vcam1 include Vegf, Il1α, and Heme oxygenase 1 (Hmox1). Vegfa and Il1a reportedly regulate Vcam1 and Il8. Hmox1 appears to be at a similar level of regulation as Il8: downstream of Vegfa and Il1α and upstream of Vcam1). Il1α strain-responsive expression could not be confirmed in subsequent follow up experiments, even using the same primer sequence and RNA samples. Kinetic analysis of Vegfa confirmed the results of the PCR array data: in neither SMCs nor MSCs was Vegfa expression significantly ($p \leq 0.05$) altered by at least 1.5-fold during the first 24 hours applied strain. In contrast, Hmox1 expression significantly increased in both cell types. Hmox1 expression in SMCs increased significantly ($p \leq 0.001$) after 6 (4.7-fold), 12 (6.4-fold), and 24 (5.1-fold) hours of applied strain. In MSCs, the magnitude of Hmox1 expression change lagged behind the response in SMCs, with significant ($p \leq 0.005$) changes after 6 (1.9-fold), 12 (2.5-fold), and 24 (2.5-fold) hours strain. Expression remained constant or decreased between 12 and 24 hours applied strain, unlike the continued changes in Il8 and Vcam1 observed during the first 24 hours applied strain. Collectively, this data indicate a Vcam1-mediated strain response may be triggered by strain-responsive molecules Il8 and Hmox1, but not by further upstream regulators Vegfa and Il1α.

3.4 Discussion

To determine whether MSCs can substitute for SMCs, signal transduction gene expression in both cell types was compared under maintenance and applied cyclic strain conditions. Signal transduction genes were robustly expressed in both cell types under maintenance and applied force conditions. Approximately 10% of genes showed strain-responsive expression levels in either one or both cell types. MSCs exhibit a muted response to cyclic strain in terms of number, magnitude, and rate of change of gene expression. In both SMCs and MSCs, expression of Il8 and Hmox1 increased, while Vcam1 expression decreased. We show that cellular response to applied force includes shared and cell type-specific components, and we add to the list of molecules with known force-responsiveness. We propose the existence of a conserved, functionally-important mechanosignaling node, based on the similarity of strain-responses across cell type and known regulatory relationships between Il8, Hmox1, and Vcam1.

This comparison of mechanosignaling is limited by the focus on the gene expression, without parallel information on protein and regulatory state. We focused on signal transduction molecules, yet other strain-responsive genes would likely be identified using transcriptome comparison. The observed response to mechanical cues may depend on other environmental factors inherent in the system, including cell culture media and underlying protein substrate [104, 103]. Altering the magnitude, frequency, or duration of applied strain may also influence subsequent signaling changes [84, 291]. Finally, mechanosignaling comparison using this method is limited by messenger RNA stability, enriching for transcripts able to withstand the sample processing [47].

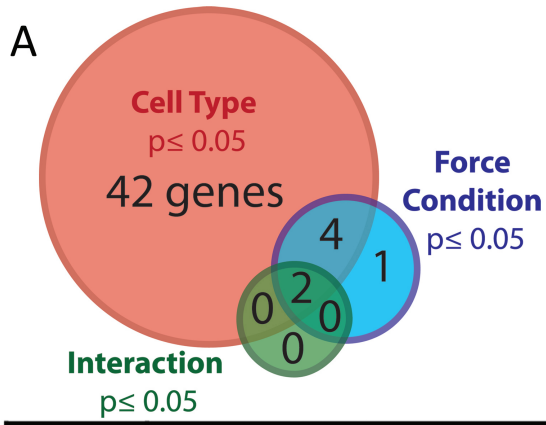
MSCs and SMCs differed markedly in their initial expression profiles, as suggested by signaling comparisons in MSC-like cell lines [35]. Significant differences in expression levels of 4 of 5 housekeeping genes indicates maintenance functions may differ between the cell types. In SMCs, genes with relatively highest expression levels (Wnt2, Rbp1, and Il8) are also associated with vascular functions. Wnt2 knock-out mice show placental vasculature defects [188]. Wnt ligands and their Frz receptors are involved in angiogenesis and

smooth muscle cell proliferation [135, 293]. Cellular retinol binding protein 1 (Rbp1) is a phenotypic marker of smooth muscle cells isolated from older donors or regions of intimal thickening [210]. Interleukin 8 (Il8, a.k.a. CXCL8) mediates inflammatory responses, acting as a chemoattractant for neutrophils and a potent angiogenic factor [241]. Genes whose expression is comparatively highest in MSCs include Vcam1, Wisp1, and En1. These genes have not been reported to have specific biological functions in MSCs. However, greater expression of these genes in MSCs compared to SMCs suggests that undifferentiated MSCs may act more like vascular cells from injured regions. This is because Vcam1 binds leukocytes and is expressed more under inflammatory and atherosclerotic conditions [203] and Wisp1 is reportedly upregulated in venous SMCs after injury [231]. Engrailed-1 has no reported vascular-specific function. These differences in initial gene expression may be due to cell type (e.g., chromatin modifications), maintenance culture media (e.g., biochemical cues), or another factor. It is not possible to distinguish between these causes based solely on this data.

After 24 hours applied strain at levels similar to that of large vessels (10%, 1 Hz), neither SMCs nor MSCs showed cellular rearrangements. This morphology is due in part to the underlying fibronectin coating, based on previous studies [67]. Cyclic strain did not result in significant changes in average signal transduction gene expression in SMCs, and slightly increased average expression levels in MSCs (1.3-fold; $p \leq 0.01$, n=3). The change in MSCs, but not SMCs, may be because SMCs were previously conditioned to cyclic strain in vivo. In spite of similar morphology and overall signal transduction gene expression, genes were identified in both cell types with expression significantly ($p \leq 0.05$, n=3) altered in strain versus static samples. More genes were identified as strain-responsive in SMCs than MSCs. Differences in initial expression levels did not account for differences in subsequent strain-responsiveness. This cell type-specific mechanosensitivity may result from differences in upstream signaling components, in spatial patterning of signaling molecules, an interaction effect of biochemical (media) and mechanical cues, or another factor.

Two-factor ANOVA comparing all static and strain samples confirmed that expression

A



B

Gene Symbol	Significance (p value)		
	Force Condition	Cell Type	Interaction
VCAM1	0.001	2.41E-09	0.021
IL8	0.004	1.32E-08	0.739
RBP1	0.007	7.18E-10	0.989
TFRC	0.010	4.48E-04	0.037
BMP4	0.019	1.84E-05	0.632
FN1	0.021	7.44E-09	0.345
MDM2	0.041	2.96E-01	0.828

Figure 10: Two-factor ANOVA of signal transduction gene responses to applied cyclic strain. Two-factor ANOVA comparing dependence of gene expression on cell type (MSCs or SMCs) and force condition (10% strain at 1 Hz or static culture). (A) Venn diagram indicating number of genes significantly dependent on cell type, force condition, and/or an interaction effect. (B) Table listing ANOVA p-values for all genes identified with significant ($p < 0.05$, n=3) force-dependent gene expression.

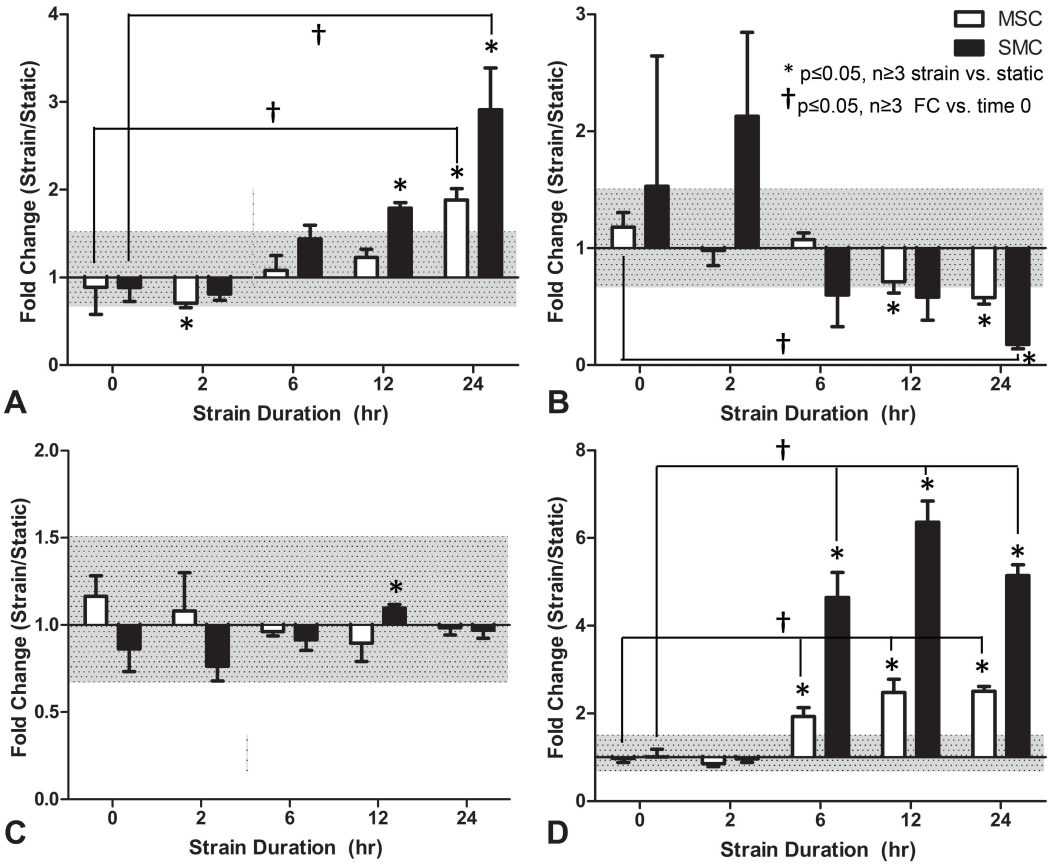


Figure 11: Expression kinetics of genes with known or predicted strain responsiveness conserved between MSCs (outlined bars) and SMCs (solid bars). Average paired fold changes (strain/static) for Il8 (A), Vcam1 (B), Vegfa (C), and Hmox1 (D) are shown based on strain and parallel static control samples harvested after 0, 2, 6, 12, or 24 hours. Error bars represent standard error of the mean. Strain vs. static samples that differ significantly ($p \leq 0.05$, $n \geq 3$) from one another based on a paired t-test are indicated by asterisks (*); fold changes after applied strain that differ significantly ($p \leq 0.05$, $n \geq 3$) from initial noise levels (0 hour data) based on an unpaired t-test are indicated by daggers (†).

of many signal transduction genes varies significantly with cell type (Figure 10). In comparison to maintenance culture conditions, though, culture in the applied strain model system decreased the number of genes that differ significantly between cell types. This suggests culture on fibronectin-coated silicone promotes more similar signaling between SMCs and MSCs than tissue culture-treated polystyrene. Culture in the strain model system also decreased overall expression levels in both cell types relative to maintenance conditions (MSCs-C_t: 27.0 vs. 28.2; SMCs-C_t: 26.7 vs. 27.1) (Figure 8). Thus biomaterials used for cell-based therapies offer one way to tune the cell signaling profile.

This data demonstrates both MSCs and SMCs can respond to cyclic strain within 6 hours with changes in message regulation. Signal transduction genes strain-sensitive in SMCs include: Cebpb, Fasn, Il1α, Irf1, Mmp7, Rbp1, TfrC, Il8, and Vcam1. In MSCs, strain-responsive signal transduction genes include: Bmp4, Hoxa1, Selplg, Il8, and Vcam1. These changes in gene expression levels are likely to be downstream targets of signaling cascades [296]. Future studies may identify which early sensors mediate the expression changes observed after hours of applied strain.

3.4.1 Strain Responses Conserved between MSCs and SMCs

Of the 84 genes assessed on the PCR arrays, only Il8 and Vcam1 were significantly strain-responsive in both MSCs and SMCs. Gene expression altered in the same direction (Il8: up; Vcam1: down) for both cell types in response to strain. The magnitude fold-change was also conserved between the two cell types, in spite of 100-fold difference in relative expression levels. Recent work has shown that cells regulate signal/noise ratios, rather than absolute levels of gene expression [82, 83]. The similarity of fold change, but not absolute expression levels, suggests Il8 and Vcam1 mechanoresponse may be controlled by a similar regulatory mechanism.

Interleukin 8 is strain-responsive in airway epithelial cells and recently in MSCs, providing evidence that mechanosensitivity of this molecule is conserved across a wide range of cell types [145, 274]. Il8 has not been previously demonstrated strain-responsive in the vascular system. The similarity of MSCs and SMCs Il8 strain-responses suggests MSCs

may be able to mimic the angiogenic and immune-related functions this molecule has in SMCs.

Vcam1 is an IgG family member whose expression is typically associated with activated endothelia [21]. Vcam1 has been shown to decrease in response to cyclic strain in endothelial cells and, recently, valvular interstitial cells [13, 263]. Vcam1 is upregulated in SMCs under inflammatory conditions [92], but no reports of strain-sensitivity in SMCs have been published. The decrease in Vcam1 observed in MSCs and SMCs, consistent with other cell types, suggests that mechanical strain at physiologic levels promotes a quiescent phenotype. Culture in the strain model system decreased Vcam1 expression for both cell types and doubled the difference in Vcam1 expression levels between cell types (Vcam1$_{strain\ system}$:127-fold vs. Vcam1$_{maintenance}$:49-fold), underscoring the importance of mechanical and material cues in determining cell signaling state.

Heme oxygenase 1 was predicted and verified as a conserved strain-responsive gene. Ontology analysis with IPA linked Hmox1 and Il8 to Vcam1 as upstream regulators. Il8 and Hmox1 reportedly increase and decrease, respectively, Vcam1 [92, 252]. The decrease in Vcam1 observed in the current study may result from the net effect of a greater increase in Hmox1 expression than Il8. The mechanism of regulation between these molecules is not known. However, similar direction and relative magnitude fold changes between cell types for all three genes suggest a common regulatory motif may exist. This may be because the function regulated by Il8/Hmox1/Vcam1 is evolutionarily important for multiple cell types. Future studies are needed to determine whether these molecules interact directly, whether an independent target regulates all three molecules, and whether signaling regulation occurs at the gene/protein levels. Furthermore, ontology software was not sufficient to predict the functional outcome of this trio of signaling changes. Functional studies could test for increased neutrophil recruitment and angiogenic potential and decreased oxidative stress and leukocyte adhesion.

3.4.2 Strain Responses Specific to SMCs

The transcription factor Cebpb contributes to immune and inflammatory responses, adipogenesis, and Collagen Type I expression [248, 18, 222]. Cebp-β has not been previously reported to be mechanosensitive. However, family member and binding partner Cebp-α decreases in umbilical cord perivascular cells in response to lower frequency equibiaxial cyclic strain (10%, 0.5 Hz for 24 hours) and Cebp family members are involved in adipogenesis, a process negatively regulated by cyclic strain [289]. The observed upregulation (2-fold) in SMCs is consistent with increased extracellular matrix synthesis in response to strain or to a change in the immune/inflammatory response state of the cells. This latter function is supported by SMCs strain-responses in other components of the Cebpb signaling network: IL8 is upregulated by Cebpb [120] and Irf1 forms a complex with Cebpb that activates the Il18 promoter [110]. The lower magnitude/significance strain-response of Cebpb in MSCs (p=0.11; FC=1.46$\pm$0.34) may be due to the activity of adipogenesis signaling pathways in this cell type.

Fasn is involved in fatty acid synthesis and oxidation reduction [183]. Fasn has not been reported to be mechanosensitive, nor is it associated with functions in the vasculature, SMCs, or MSCs. Fasn is upregulated in many human tumors [183]. Its role in lipogenesis, an important function regardless of organ type, suggests its signaling is regulated in all cells. These data show Fasn is strain-responsive in SMCs (FC=1.52$\pm$0.22; p=0.041), but not MSCs. Long-chain fatty acids affect atherogenesis [59]. Follow-up studies in SMCs could test whether increased Fasn expression correlates with other markers of atherosclerosis.

IL1α was identified as strain-sensitive by the PCR arrays, yet follow up qPCR studies using the same primer and RNA samples could not confirm this result. This may be because the IL1α transcript is less stable or because the array results are a false positive.

The transcription factor Irf1 regulates interferon alpha and beta, as well as their downstream targets [176]. It regulates apoptosis, tumor suppression, and iNos signaling. Irf1, in

addition to regulating Il8 expression, also regulates Vcam1 expression [206]. Mechanoregulation of Irf1 expression has not been reported. Irf1 is significantly upregulated in SMCs exposed to cyclic strain, but does not change in MSCs. MSCs and SMCs express virtually the same amount of Irf1 under maintenance culture, suggesting gene expression may not be inherently force-responsive, but can be a downstream indicator of another force-sensing mechanism.

Mmp7 is an extracellular matrix protease targeting proteoglycans, fibronectin, elastin, and casein. Mmp7 has no reported strain-sensitivity, although one study reports an increase in MMP7 protein levels after culture in a rapid flow bioreactor [257]. Mmp7 expression has not been reported in MSCs, but is expressed in some instances in SMCs [68, 123]. Mmp7 expression decreases significantly in SMCs, but does not significantly change in MSCs. The greater variation in Mmp7 expression in strain versus static or maintenance cultures suggests physical force may affect the stringency of signaling regulation, as well as overall levels.

Rbp1 is a carrier protein involved in retinol transport and a marker of SMCs wound healing [318]. Rbp1 is associated with neither mechanosensitivity nor expression in MSCs. Rbp1 decreases in both cell types in response to strain, but is only significant in SMCs (p_{SMCs}=0.003 vs. p_{MSCs}=0.246).

TfrC, also known as CD71, is a protein surface marker used to characterize MSCs [226]. TfrC does not alter expression in MSCs exposed to cyclic strain, but is significantly upregulated in SMCs. No characteristic function has been described for Tfrc in SMCs, MSCs, or the vasculature.

3.4.3 Strain Responses Specific to MSCs

Bmp4 is involved in MSCs differentiation towards osteocytes, adipocytes, and smooth muscle-like cells [325]. In addition, Bmp4 is upregulated in cases of oscillatory flow and atherogenesis [266, 119]. Bmp4 decreases in both cell types, but only significantly in MSCs. Down-regulation of Bmp4 in response to a physiological mechanical cue is consistent with relatively lower Bmp4 expression under physiological flow conditions compared

to low, oscillatory or calcified regions.

Homeobox A1, Hoxa1, is a transcription factor involved in embryonic development including gene regulation, morphogenesis, and differentiation. Non-lethal mutations in Hoxa1 result in vascular malformations [283]. Hoxa1 is not associated with particular functions in adult organism MSCs or SMCs. Hoxa1 is expressed in MSCs at higher levels and is downregulated in response to strain, compared to lower and constant Hoxa1 expression levels in SMCs. The initial higher levels and subsequent decrease in Hoxa1 expression in MSCs may be related to the initial stem cell state of the cells, followed by partial differentiation due to mechanical cues.

The last gene identified as strain-responsive by paired t-test analysis is P-selectin ligand, Selplg. Selplg is expressed at high levels and increases in response to strain, compared with lower and constant expression levels in SMCs. Selplg binds activated platelets and endothelia and are involved in inflammation and atherosclerosis [298]. Selplg is not associated with particular functions in MSCs, nor has it been previously reported as strain-responsive. Higher expression in MSCs suggests these cells may bind more tightly than SMCs in inflamed or injured areas (P-selectin+). Since Selplg is expressed on immune related cells, myeloid cells and stimulated T lymphocytes, MSCs binding to P-selectin receptors may be one means by which MSCs modulate the local immune response.

3.5 Conclusions

Few studies have been completed to determine signaling changes in SMCs due to applied cyclic strain. Thus, this study contributes to our knowledge of SMCs biology. This work highlights conserved and cell type-specific genes involved in the strain response of MSCs and SMCs. Overall, MSCs show reduced number, magnitude and speed of gene expression change, relative to SMCs. This may be because they are not fully differentiated, or because strain-sensitivity is a particular characteristic of SMCs. Before using MSCs as a SMCs substitute, we need to determine which features of SMCs signaling are most important for MSCs to successfully replicate. This data suggests MSCs may enable similar immune and inflammatory-related signaling, but will not match many other aspects

of SMCs strain-response. This data also suggests MSCs may adhere more to sites of vascular injury than SMCs, due to increased P-selectin adhesion.

Based on comparisons in this study, we propose that mechanosensing occurs via a combination of evolutionarily-conserved signaling changes and cell type-specific changes. We use semi-high throughput PCR arrays to identify novel strain-responsive genes and bioinformatics analysis to successfully predict mechanoresponsive molecules. Through specific gene examples, we demonstrate that: (a) strain responses can be conserved via absolute or relative (fold change) level of gene expression, (b) strain-responses are determined via combinations of multiple factors, not merely the level of initial gene expression, and (c) functionally important mechanoresponses may also be regulated through sample variance, as in the case of Mmp7. Identifying conserved aspects and critical parameters governing cellular mechanoresponse will improve our ability to understand the causes of disease and to design cell-based therapies that account for mechanical manipulations.

3.6 Materials and Methods

Supplies Cells and culture media were purchased from Lonza. PCR arrays and associated materials were purchased from SA Biosciences. Standard qPCR reagents were purchased from Qiagen (RNA isolation), Invitrogen (cDNA synthesis), and ABI (qPCR mastermix).

Cell culture of MSCs & SMCs Human adult bone marrow-derived mesenchymal stem cells and aortic smooth muscle cells were cultured according to manufacturer's recommendations (Lonza). MSCs were expanded to Passage 6 and characterized for expression of protein surface markers and differentiation potential along osteogenic, chondrogenic, and adipogenic lineages prior to experimental use. SMCs expanded to Passage 3 were used for experiments.

Applied strain Equibiaxial cyclic strain was applied using a custom-built device [267]. Briefly, cells were seeded on etched, protein-coated silicone membranes at 10,000 cells/cm^2, calculated using a Coulter Counter Multisizer 3. For each membrane holder chamber (MHC), cells were allowed to attach in 2 ml media for four hours at 37·C, prior to addition

of media up to 25 ml final volume and static preconditioning culture on the silicone substrate for 48 hours total. Samples were subsequently exposed to defined applied strain (10%, 1 Hz) or parallel static culture for $\leq$24 hours. To assess cell morphology, phase images of samples were taken using an Axiovert microscope (Zeiss) immediately prior to and following exposure to mechanical force.

PCR Array assessment RNA was isolated according to manufacturer's instructions (Qiagen) and quantified using a NanoDrop spectrophotometer, followed by cDNA synthesis and PCR array assessment according to SA Biosciences guidelines. PCR arrays were analyzed using a MyiQ thermal cycler (Bio-Rad). All arrays (n=18) passed the human genomic DNA control (Supplemental Fig 12) and PCR efficiency control included on the arrays. Relative expression values for each gene of interest (GOI) were calculated using the $\Delta\Delta$C$_\mathrm{t}$ method $(C_\mathrm{t}(GOI_\mathrm{strain}) - C_\mathrm{t}(\overline{HKPG}_\mathrm{strain}))/(C_\mathrm{t}(GOI_\mathrm{static}) - C_\mathrm{t}(\overline{HKPG}_\mathrm{static}))$. C$_\mathrm{t}(\overline{HKPG})$ was determined using five housekeeping genes included on the PCR arrays (Supplemental Table 3). Normalization to housekeeping genes, fold change, and statistical calculations were completed using custom scripts in Matlab (Mathworks, Inc.). Signaling analysis was completed in part using the manually-curated bioinformatics software, Ingenuity Pathways Analysis (Ingenuity). To identify connections and predict additional strain-responsive molecules, an input gene list including identified strain-responsive (|FC|$\geq$1.5, $p \leq 0.05$) genes, genes culled from the literature as strain-responsive in SMCs under similar conditions, and genes important for immune and inflammatory responses in the vasculature was analyzed in IPA.

Standard qPCR assessment Individual genes were assessed using standard qPCR. RNA was isolated from kinetic experiments and quantified as above, followed by cDNA synthesis using a FirstStrand III SuperScript Kit (Invitrogen) and PCR reaction with Power SYBR Green mastermix (ABI). qPCR samples were run on a StepOne Plus machine (ABI) and baseline-subtracted C$_\mathrm{t}$ analyzed in Excel (Microsoft). All data were converted to molar concentrations using a standard curve and normalized to Gapdh expression. Two fold-changes were calculated: a strain response (the ratio of strain/static relative expression) and a cell type response (ratio of MSCs/SMCs expression under respective maintenance

conditions). A 1.5-fold change threshold was used to identify strain-responsive genes.

Statistical analysis Maintenance comparisons were completed using unpaired t-tests. Static and strain samples were compared using paired t-tests and two-factor ANOVA with post-hoc Tukey tests. Unless otherwise stated, significance is defined as $p \leq 0.05$. PCR arrays were completed in triplicate for each group, with each array representing data from four pooled independent samples from a single independent experiment. Temporal kinetics assessments were completed for n=3-4, with each replicate representing a single sample from an independent experiment. A randomized experimental design was used to minimize bias due to experimental variability.

3.7 Supplemental Figures and Tables

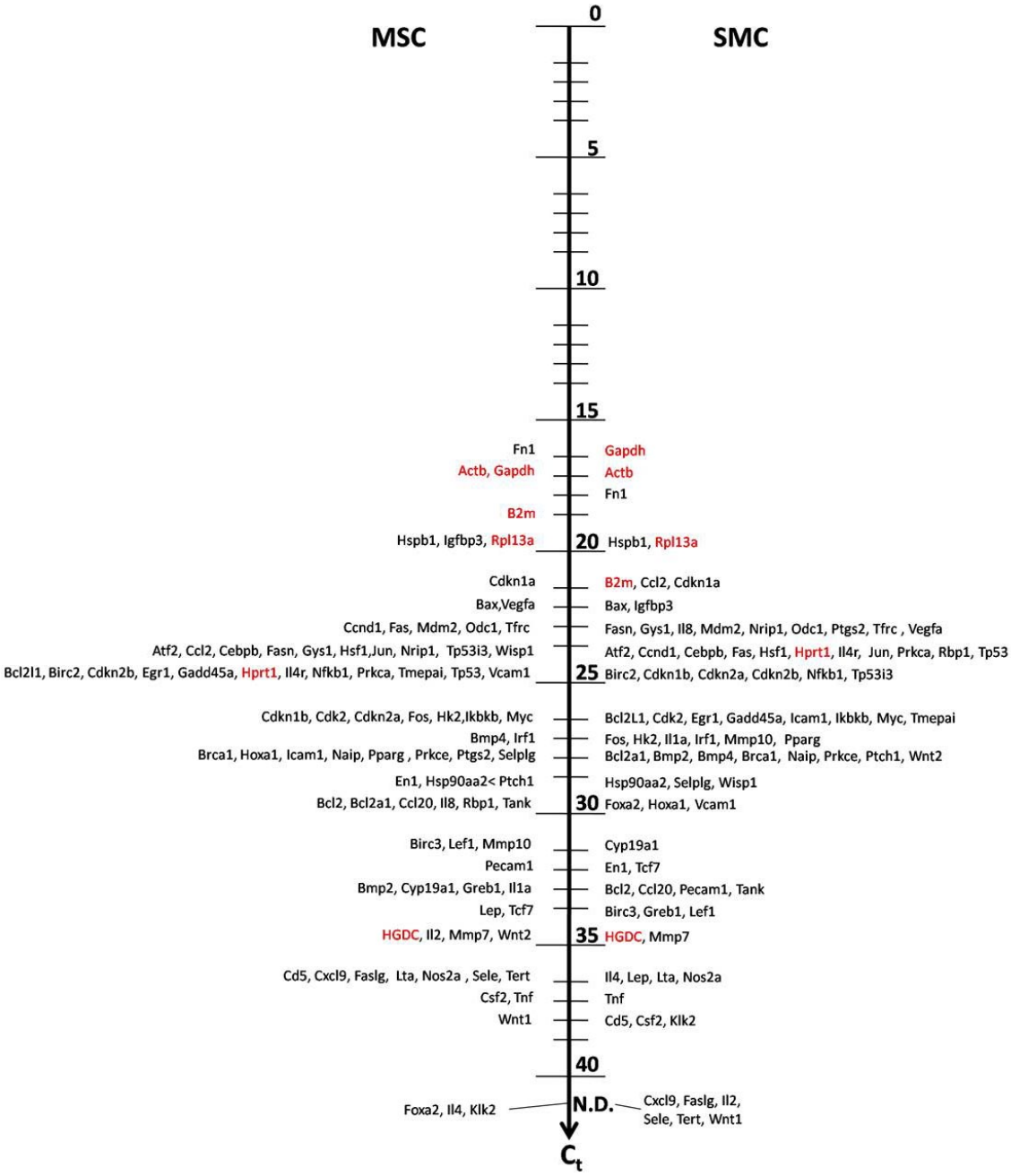


Figure 12: Supplemental Figure. Detection of genes in MSCs and SMCs under maintenance culture conditions. Black text = signal transduction genes. Red text = housekeeping genes or human genomic DNA control.

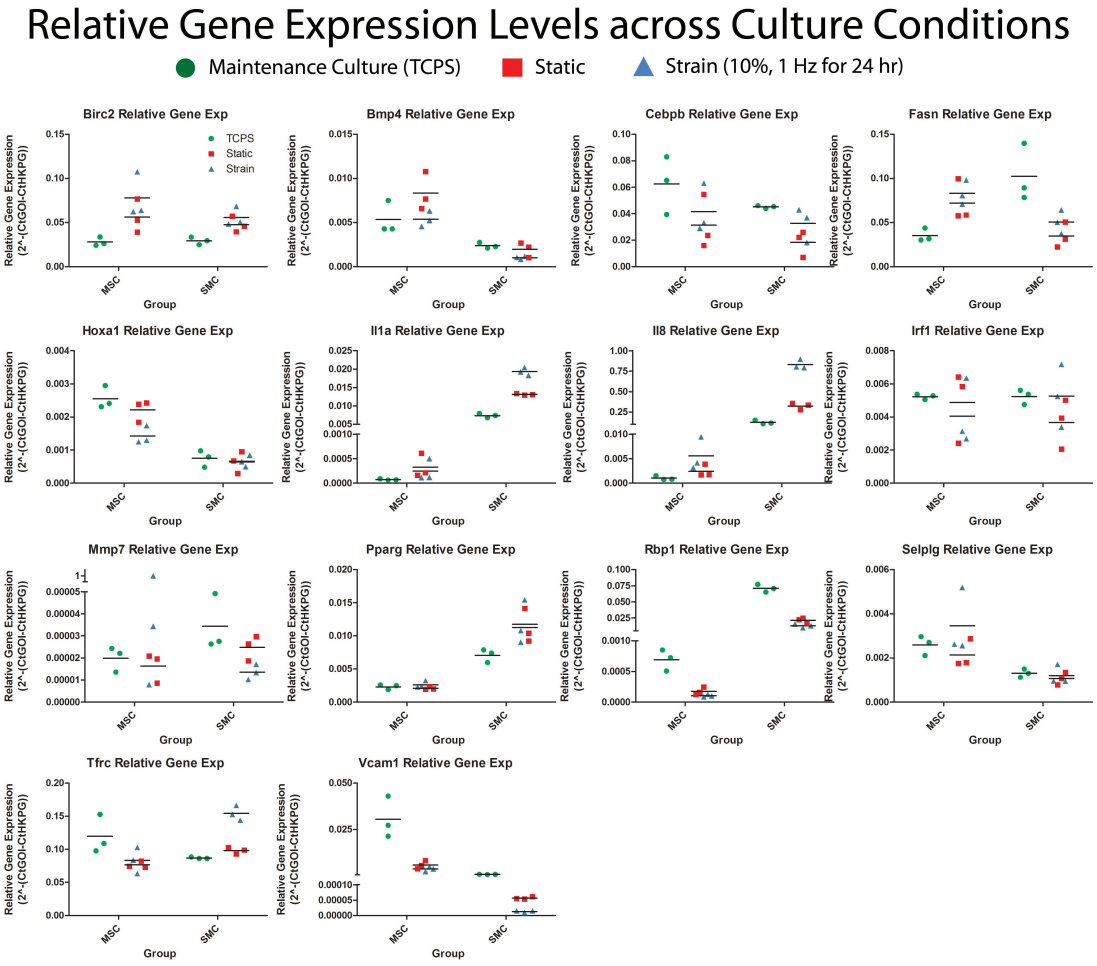


Figure 13: Supplemental Figure 2. Relative gene expression levels for genes identified as cyclic strain responsive using one or more methods. Relative gene expression (2-$\triangle C_t$) values for three experimental replicates are shown for MSCs (left) and SMCs (right) under maintenance culture (green circles), static control conditions (red squares) and after 24 hours applied cyclic strain (10%, 1 Hz) (blue triangles). Genes shown are those identified as strain-responsive by either paired t-test or ANOVA, specifically: (A) Bmp4, (B) Cebpb, (C) Fasn, (D) Fn1, (E) Hoxa1, (F) Il1a, (G) Il8, (H) Irf1, (I) Mdm2, (J) Mmp7, (K) Rbp1, (L) Selplg, (M) Tfrc, and (N) Vcam1. Three PCR arrays per sample group.

Table 2: Table of gene expression responses to applied cyclic strain. Results for each cell type are presented in terms of a fold change (ratio of strain/static relative gene expression) and standard deviation and significance based on a paired t-test. Overall dependence of gene expression on force condition, cell type, or an interaction effect of force condition and cell type is shown as significance values from a two-factor ANOVA. P-values identified as significant ($p \leq 0.05$, n=3) are shown in blue, bold text.

Gene Symbol	Paired T-test Results						Two-factor ANOVA Results		
	MSC			SMC			Post-hoc significance		
	Avg. Paired Fold Change	Standard Deviation	p-Value	Avg. Paired Fold Change	Standard Deviation	p-Value	Cell Type	Force Condition	Interaction
Signal Transduction Genes									
ATF2	0.94	0.27	0.634	1.12	0.33	0.694	**0.006**	0.989	0.419
BAX	1.05	0.12	0.537	1.31	0.39	0.282	0.117	0.405	0.574
BCL2	2.14	2.58	0.744	1.34	0.57	0.423	**0.018**	0.653	0.983
BCL2A1	1.09	0.25	0.670	1.06	0.30	0.853	**0.000**	0.790	0.923
BCL2L1	1.13	0.16	0.301	1.40	0.58	0.338	**0.000**	0.526	0.786
NAIP	0.91	0.35	0.571	1.12	0.24	0.492	**0.005**	0.870	0.331
BIRC2	1.40	0.19	0.054	1.18	0.11	0.103	0.174	0.146	0.587
BIRC3	1.03	0.38	0.949	0.93	0.75	0.560	**0.000**	0.492	0.512
BMP2	0.58	0.18	0.106	1.06	0.55	0.933	**0.000**	0.267	0.309
BMP4	0.65	0.06	**0.016**	0.57	0.20	0.085	**0.000**	**0.019**	0.632
BRCA1	1.08	0.45	0.921	1.14	0.17	0.288	**0.000**	0.654	0.766
CCL2	1.49	0.46	0.189	1.16	0.31	0.502	**0.000**	0.069	0.337
CCL20	1.77	1.21	0.384	2.30	0.79	0.057	**0.009**	0.090	0.569
CCND1	1.33	0.44	0.310	1.38	0.32	0.141	**0.008**	0.275	0.916
CD5	1.95	2.08	0.838	1.19	N/A	N/A	N/A	N/A	N/A
CDK2	0.91	0.20	0.470	1.02	0.18	0.950	0.085	0.744	0.710
CDKN1A	1.13	0.21	0.444	1.18	0.12	0.110	**0.002**	0.245	0.809
CDKN1B	1.11	0.18	0.427	1.06	0.21	0.762	0.212	0.698	0.883
CDKN2A	0.97	0.19	0.727	1.08	0.09	0.253	**0.004**	0.916	0.693
CDKN2B	1.12	0.34	0.749	0.91	0.16	0.403	N/A	N/A	N/A
CEBPB	1.46	0.34	0.113	1.97	0.53	**0.047**	0.265	0.160	0.664
CSF2	2.08	N/A	N/A	1.91	1.07	0.381	N/A	N/A	N/A
CXCL9	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CYP19A1	1.10	N/A	N/A	0.81	0.11	0.110	N/A	N/A	N/A
EGR1	1.27	0.52	0.474	1.32	0.46	0.346	**0.003**	0.318	0.907
EN1	0.84	0.25	0.342	1.03	0.34	1.000	**0.000**	0.485	0.485
FAS	1.07	0.34	0.855	1.11	0.20	0.476	**0.016**	0.671	0.850
FASLG	N/A	N/A	N/A	0.64	N/A	N/A	N/A	N/A	N/A
FASN	1.20	0.21	0.238	1.52	0.22	**0.041**	**0.007**	0.135	0.511
FN1	1.19	0.16	0.189	1.41	0.16	**0.036**	**0.000**	**0.021**	0.345
FOS	1.29	0.78	0.774	1.11	0.21	0.529	0.631	0.749	0.962
FOXA2	N/A	N/A	N/A	0.92	0.29	0.606	N/A	N/A	N/A
GADD45A	1.56	0.66	0.254	1.11	0.07	0.103	0.506	0.338	0.580
GREB1	1.83	1.99	0.927	1.34	0.03	**0.032**	N/A	N/A	N/A
GYS1	1.12	0.23	0.497	1.07	0.20	0.654	0.120	0.664	0.909
HK2	1.44	0.63	0.396	1.49	0.41	0.171	0.527	0.274	0.902
HOXA1	0.64	0.09	**0.034**	1.21	0.51	0.690	**0.001**	0.452	0.198
HSF1	1.10	0.14	0.349	1.25	0.35	0.342	0.072	0.173	0.608
HSPB1	0.90	0.31	0.561	1.01	0.12	0.928	**0.000**	0.422	0.380
HSP90AA2	1.43	1.00	0.649	1.28	0.13	0.060	0.087	0.169	0.902
ICAM1	0.90	0.49	0.584	1.09	0.12	0.322	**0.003**	0.865	0.671
IGFBP3	0.76	0.15	0.125	0.95	0.10	0.431	**0.000**	0.229	0.412
IKBKB	1.41	0.29	0.129	1.15	0.26	0.414	0.137	0.199	0.556
IL1A	0.70	0.13	0.082	1.47	0.11	**0.012**	**0.000**	0.984	0.269
IL2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
IL4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
IL4R	1.03	0.13	0.766	1.03	0.12	0.729	**0.000**	0.678	0.982
IL8	2.24	0.35	**0.014**	2.59	0.31	**0.006**	**0.000**	**0.004**	0.739
IRF1	0.88	0.31	0.521	1.47	0.16	**0.026**	0.965	0.711	0.327
JUN	1.32	0.46	0.376	1.28	0.53	0.479	0.234	0.555	0.957
KLK2	0.55	N/A	N/A	0.14	N/A	N/A	N/A	N/A	N/A
LEF1	4.18	3.20	0.371	0.96	0.60	0.677	0.275	0.413	0.197
LEP	N/A	N/A	N/A	0.21	N/A	N/A	N/A	N/A	N/A
LTA	0.78	0.13	0.282	2.69	2.83	0.651	N/A	N/A	N/A
MDM2	1.22	0.15	0.112	1.28	0.20	0.128	0.296	**0.041**	0.828
MMP10	0.73	0.49	0.328	1.24	0.21	0.175	**0.000**	0.671	0.278
MMP7	1.02	0.88	0.818	0.54	0.03	**0.004**	N/A	N/A	N/A
MYC	1.66	0.54	0.140	1.70	0.56	0.107	**0.022**	0.084	0.956
NFKB1	1.13	0.11	0.161	1.10	0.16	0.398	0.266	0.320	0.877
NOS2A	1.24	N/A	N/A	1.05	N/A	N/A	N/A	N/A	N/A
NRIP1	1.10	0.17	0.435	1.35	0.20	0.074	**0.000**	0.091	0.323
ODC1	1.32	0.54	0.416	1.57	0.34	0.084	**0.000**	0.084	0.545
PECAM1	1.32	0.75	0.708	1.28	0.26	0.198	0.655	0.680	0.934
PPARG	1.25	0.12	0.056	1.08	0.37	0.875	**0.000**	0.316	0.458
PRKCA	1.32	0.42	0.300	1.16	0.35	0.539	**0.004**	0.184	0.642
PRKCE	1.27	0.49	0.487	1.38	0.53	0.353	0.054	0.356	0.868
PTCH1	1.58	0.64	0.198	1.75	0.43	0.067	0.630	0.095	0.805
PTGS2	1.01	0.20	0.997	1.24	0.07	**0.020**	**0.000**	0.430	0.428
RBP1	0.66	0.34	0.246	0.60	0.03	**0.003**	**0.000**	**0.007**	0.989
SELE	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SELPLG	1.58	0.20	**0.024**	1.12	0.21	0.474	**0.002**	0.183	0.378
TANK	0.90	0.43	0.560	0.79	0.35	0.396	**0.000**	0.164	0.677
TCF7	1.08	0.54	0.989	0.78	0.30	0.361	0.977	0.699	0.691
TERT	N/A	N/A	N/A	1.40	N/A	N/A	N/A	N/A	N/A
TFRC	1.08	0.21	0.628	1.58	0.15	**0.016**	**0.000**	**0.010**	**0.037**
TMEPAI	0.88	0.31	0.497	0.91	0.08	0.169	**0.011**	0.331	0.790
TNF	2.09	1.69	0.561	0.63	0.50	0.323	N/A	N/A	N/A
TP53	0.96	0.17	0.637	1.11	0.07	0.093	0.348	0.869	0.597
TP53I3	1.31	0.40	0.290	1.03	0.34	1.000	**0.000**	0.447	0.447
VCAM1	0.62	0.04	**0.007**	0.23	0.07	**0.016**	**0.000**	**0.001**	**0.021**
VEGFA	1.34	0.61	0.574	1.30	0.11	**0.032**	**0.017**	0.478	0.937
WISP1	0.96	0.21	0.706	0.73	0.14	0.109	**0.000**	0.200	0.356
WNT1	1.69	1.94	0.997	0.72	N/A	N/A	N/A	N/A	N/A
WNT2	0.71	0.27	0.218	0.91	0.27	0.581	**0.010**	0.467	0.700
Housekeeping Genes									
B2M	1.01	0.07	0.848	1.01	0.10	0.887	**0.000**	0.885	0.997
HPRT1	0.97	0.09	0.617	0.94	0.12	0.494	**0.000**	0.546	0.834
RPL13A	0.90	0.09	0.220	1.13	0.04	**0.029**	0.666	0.949	0.296
GAPDH	1.20	0.21	0.228	1.02	0.07	0.654	**0.000**	0.281	0.389
ACTB	0.97	0.23	0.783	0.92	0.10	0.299	**0.002**	0.695	0.904

Table 3: Table of genes included on Signal Transduction PathwayFinder^{TM} PCR Array (SA Biosciences). Gene identification information for 84 signal transduction genes and 5 housekeeping genes included on human Pathway Finder^{TM} Signal Transduction PCR array (modified from SA Biosciences Gene Table). Control wells included on array but not listed in this table include: a single well to assess human genomic DNA contamination (HGDC), triplicate wells assessing a positive PCR control to verify the qPCR amplification (PPC), and triplicate wells assessing a reverse transcription control verifying cDNA synthesis (RTC).

Symbol	Gene Name	Description	GenBank Accession Number
SIGNAL TRANSDUCTION GENES			
ATF2	CRE-BP1/CREB2	Activating transcription factor 2	NM_001880
BCL2	Bcl-2	B-cell CLL/lymphoma 2	NM_000633
BCL2A1	ACC-1/ACC-2	BCL2-related protein A1	NM_004049
BCL2L1	BCL-XL/S	BCL2-like 1	NM_138578
NAIP	BIRC1/NLRB1	NLR family, apoptosis inhibitory protein	NM_004536
BIRC2	API1/HIAP2	Baculoviral IAP repeat-containing 2	NM_001166
BIRC3	AIP1/API2	Baculoviral IAP repeat-containing 3	NM_001165
BMP2	BMP2A	Bone morphogenetic protein 2	NM_001200
BMP4	BMP2B/BMP2B1	Bone morphogenetic protein 4	NM_130851
BRCA1	BRCAI/BRCC1	Breast cancer 1, early onset	NM_007294
CCL2	GDCF-2/GDCF-2 HC11	Chemokine (C-C motif) ligand 2	NM_002982
CCL20	CKb4/LARC	Chemokine (C-C motif) ligand 20	NM_004591
CCND1	BCL1/D11S287E	Cyclin D1	NM_053056
CDK2	p33(CDK2)	Cyclin-dependent kinase 2	NM_001798
CDKN1A	CAP20/CDKN1	Cyclin-dependent kinase inhibitor 1A (p21, Cip1)	NM_000389
CDKN1B	CDKN4/KIP1	Cyclin-dependent kinase inhibitor 1B (p27, Kip1)	NM_004064
CDKN2A	ARF/CDK4I	Cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)	NM_000077
CDKN2B	CDK4I/INK4B	Cyclin-dependent kinase inhibitor 2B (p15, inhibits CDK4)	NM_004936
CEBPB	C/EBP-beta	CCAAT/enhancer binding protein (C/EBP), beta	NM_005194
CYP19A1	ARO/ARO1	Cytochrome P450, family 19, subfamily A, polypeptide 1	NM_000103
EGR1	AT225/G0S30	Early growth response 1	NM_001964
EN1	Engrailed 1	Engrailed homeobox 1	NM_001426
FAS	ALPS1A/APO-1	Fas (TNF receptor superfamily, member 6)	NM_000043
FASN	FAS/OA-519	Fatty acid synthase	NM_004104
FN1	CIG/DKFZp686F10164	Fibronectin 1	NM_002026
FOS	c-fos	V-fos FBJ murine osteosarcoma viral oncogene homolog	NM_005252
GADD45A	DDIT1/GADD45	Growth arrest and DNA-damage-inducible, alpha	NM_001924
GYS1	GSY/GYS	Glycogen synthase 1 (muscle)	NM_002103
HK2	DKFZp686M1669/HKII	Hexokinase 2	NM_000189
HOXA1	BSAS/HOX1	Homeobox A1	NM_005522
HSPB1	CMT2F/DKFZp586P1322	Heat shock 27kDa protein 1	NM_001540
ICAM1	BB2/CD54	Intercellular adhesion molecule 1 (CD54), human rhinovirus receptor	NM_000201
IGFBP3	BP-53/IBP3	Insulin-like growth factor binding protein 3	NM_000598
IKBKB	IKK-beta/IKK2	Inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta	NM_001556
IL1A	IL-1A/IL1	Interleukin 1, alpha	NM_000575
IL4R	CD124/IL4RA	Interleukin 4 receptor	NM_000418
IL8	3-10C/AMCF-I	Interleukin 8	NM_000584
IRF1	IRF-1/MAR	Interferon regulatory factor 1	NM_002198
LEF1	DKFZp586H0919/TCF1ALPHA	Lymphoid enhancer-binding factor 1	NM_016269
LEP	OB/OBS	Leptin	NM_000230
MDM2	HDMX/hdm2	Mdm2, transformed 3T3 cell double minute 2, p53 binding protein (mouse)	NM_002392
MMP10	SL-2/STMY2	Matrix metallopeptidase 10 (stromelysin 2)	NM_002425
MMP7	MMP-7/MPSL1	Matrix metallopeptidase 7 (matrilysin, uterine)	NM_002423
MYC	c-Myc	V-myc myelocytomatosis viral oncogene homolog (avian)	NM_002467
NFKB1	DKFZp686C01211/EBP-1	Nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 (p105)	NM_003998
NRIP1	RIP140	Nuclear receptor interacting protein 1	NM_003489
ODC1	Ornithine decarboxylase	Ornithine decarboxylase 1	NM_002539
PPARG	NR1C3/PPARG1	Peroxisome proliferator-activated receptor gamma	NM_015869
PRKCA	AAG6/PKC-alpha	Protein kinase C, alpha	NM_002737
PTCH1	BCNS/HPE7	Patched homolog 1 (Drosophila)	NM_000264
PTGS2	COX-2/COX2	Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)	NM_000963
RBP1	CRABP-I/CRBP	Retinol binding protein 1, cellular	NM_002899
SELPLG	CD162/CLA	Selectin P ligand	NM_003006
TANK	I-TRAF/TRAF2	TRAF family member-associated NFKB activator	NM_004180
TCF7	TCF-1	Transcription factor 7 (T-cell specific, HMG-box)	NM_003202
TFRC	CD71/TFR	Transferrin receptor (p90, CD71)	NM_003234
TMEPAI	PMEPA1/STAG1	Transmembrane, prostate androgen induced RNA	NM_020182
TP53	LFS1/TRP53	Tumor protein p53	NM_000546
TP53I3	PIG3	Tumor protein p53 inducible protein 3	NM_004881
VCAM1	CD106/DKFZp779G2333	Vascular cell adhesion molecule 1	NM_001078
VEGFA	VEGF/VEGF-A	Vascular endothelial growth factor A	NM_003376
WISP1	CCN4/WISP1c	WNT1 inducible signaling pathway protein 1	NM_003882
WNT2	INT1L1/IRP	Wingless-type MMTV integration site family member 2	NM_003391
HOUSEKEEPING GENES & INTERNAL CONTROLS			
B2M	B2M	Beta-2-microglobulin	NM_004048
HPRT1	HGPRT/HPRT	Hypoxanthine phosphoribosyltransferase 1 (Lesch-Nyhan syndrome)	NM_000194
RPL13A	RPL13A	Ribosomal protein L13a	NM_012423
GAPDH	G3PD/GAPD	Glyceraldehyde-3-phosphate dehydrogenase	NM_002046
ACTB	PS1TP5BP1	Actin, beta	NM_001101

Table 4: Table of cell type-dependent signal transduction gene expression. Significance ($p \leq 0.05$, n=3) based on unpaired t-test for maintenance culture conditions or two-factor ANOVA for strain model system (strain and parallel static controls for both cell types). 47 of 84 signal transduction genes have significant ($p \leq 0.05$, n=3) differences in expression between MSCs and SMCs under at least one culture condition. Expression of 4 of 5 housekeeping genes differs between cell types in both maintenance and strain model system culture. [1]Significant interaction effect between cell type and force condition. [2]No comparison with strain model system possible due to insufficient data set for ANOVA.

CELL TYPE-DEPENDENT SIGNAL TRANSDUCTION GENES		
Significant Under Maintenance Culture and Strain Model System		
BCL2A1	HOXA1	PPARG
BCL2L1	HSPB1	PRKCA
BIRC3	ICAM1	PTGS2
BMP2	IGFBP3	RBP1
BMP4	IL1A	SELPLG
CCL2	IL4R	TANK
CDKN2A	IL8	TP53I3
EN1	MMP10	VCAM1[1]
FN1	NRIP1	WISP1
Significant Only Under Maintenance Culture		
BCL2	FASN	TCF7
CCL20	GADD45A	TP53
CCND1	GYS1	WNT2
CYP19A1	LEF1	CDKN2B[2]
FAS	PTCH1	LEP[2]
Significant Only Under Strain Model System		
BRCA1	EGR1	TFRC[1]
CDKN1A	ODC1	
CELL TYPE-DEPENDENT HOUSKEEPING GENES		
Significant Under Maintenance Culture and Strain Model System		
ACTB	GAPDH	
B2M	HPRT1	

Table 5: Table summarizing genes with significant ($p < 0.05$) expression differences due to applied strain. Genes were classified as significant based on one or more of the following statistical tests: paired t-test of MSCs, paired t-test of SMCs, or two-factor ANOVA. Genes shown include those both up- or down-regulated in response to strain.

STRAIN-REPONSIVE SIGNAL TRANSDUCTION GENES		
Significant in SMC and MSC Paired T-test and ANOVA		
IL8	VCAM1	
Significant Only in SMC Paired T-test		
CEBPB	IRF1	TFRC
FASN	MMP7	
IL1A[1]	RBP1	
Significant Only in MSC Paired T-test		
BMP4[1]	HOXA1	SELPLG
Significant Only Using Two-Factor ANOVA		
MDM2		
STRAIN-REPONSIVE HOUSKEEPING GENES		
Significant in SMC or MSC Paired T-Test or ANOVA		
N/A		

CHAPTER IV

TRANSCRIPTOME RESPONSES OF MESENCHYMAL STEM CELLS AND AORTIC SMOOTH MUSCLE CELLS TO APPLIED EQUIBIAXIAL CYCLIC STRAIN

4.1 Abstract

Both mesenchymal stem cells (MSCs) and smooth muscle cells (SMCs) respond to equibiaxial cyclic strain with gene expression signaling changes within 24 hours. Few studies have analyzed the transcriptome response of SMCs to cyclic strain, though, and assessments of MSCs response to cyclic strain have focused on differentiation towards SMCs. To more broadly determine the similarities and differences of gene-based cyclic strain responses in MSCs and SMCs, we analyzed cells seeded on fibronectin-coated silicone and exposed to either equibiaxial cyclic strain (10%, 1 Hz) or parallel static culture for 24 hours using whole human genome microarrays (Agilent). MSCs and SMCs overall expression profiles differ primarily in terms of cell type, with less marked profile shifts due to force condition, based on principal component analysis and two-factor ANOVA. Two-tailed paired t-tests and two-factor ANOVA were used to identify genes statistically significantly altered in response to applied force. Strain-responsive genes (paired t-test: $p < 0.05$, n=3 and $|FC| > 1.5$) were present in both cell types, albeit more numerous and lower average fold change in MSCs compared to SMCs. Gene expression sensitive to mechanical strain primarily affected molecules in the cytoplasm or nucleus, and altered oxidative stress, protein binding, and ferritin signaling. MSCs and SMCs differ markedly in their initial and strain-responsive transcriptomes, yet share a subset of strain-responses across cell types. This analysis provides a foundation for targeted future mechanosensitivity comparisons between cell types.

4.2 Background

DNA microarrays can be used to simultaneously track expression level changes in thousands of genes [246]. Gene expression is an energy-intensive, multi-step, and highly regulated process [303]. Changes in related gene expression levels that are statistically significant and of magnitude above a detection threshold correlate with functional changes in cell behavior due to a treatment [196]. Combining expression data for multiple genes with the database of information about molecular signaling and function triangulates on physiologic processes most frequently triggered by the altered genes. We employed this tool to study cellular response to applied cyclic strain, comparing aortic smooth muscle and mesenchymal stem cell transcriptomes exposed to equibiaxial cyclic strain (10%, 1 Hz) or parallel static culture. We hypothesize that comparisons across disparate cell types and use of high-throughput data will highlight broad features of cellular mechanoresponse.

High-throughput approaches have been applied to smooth muscle cells to screen chemical libraries for affects on angiogenesis or SMCs contraction [72, 320]; characterize cell-biomaterial interactions [3]; track oxidative stress, collagen assembly, or changes in membrane potential [242, 121, 311]; and sequence novel receptors [102]. One high-throughput technology, cDNA microarrays, has been used to study many aspects of smooth muscle cell biology. Two microarray studies focused on SMCs signaling responses to applied cyclic strain using microarrays [73, 140]. Feng *et al* applied equibiaxial cyclic strain (4%, 1 Hz for 12 or 24 hours) to human aortic SMCs cultured on fibronectin-coated surfaces and identified a small subset of genes altered in response to strain. More recently, Kona *et al* analyzed the synergistic effects of cyclic strain (10%, 1 Hz for 3 days) and growth factor stimulation. Kona *et al* report that cyclic strain increased inflammatory gene expression and decreased proliferation and apoptosis-related genes.

Although a newer field, MSCs have also been studied using high-throughput techniques. Perhaps due to the popularity of stem cell-based therapies and relative ease of culture of MSCs, these cells are often used in proof-of-principle experiments for development of new technologies. These high-throughput techniques include tissue printing

approaches [219], culture environment tests of surface or media modifications [138, 40], and high-throughput differentiation [240]. More than 150 reports have analyzed gene expression using high-throughput microarrays to assess MSCs. These microarray comparisons focus on transcriptional changes of MSCs-like cells derived from different sources [285, 301]; of undifferentiated MSCs with MSCs differentiated towards osteogenic, chondrogenic, adipogenic, and neuronal lineages ; and different culture conditions [254]. Only three studies have investigated the effects of applied force on mesenchymal stem cells [81, 148, 218]. These studies indicate MSCs response to force varies with the type of mechanical cue: gene expression changes in MSCs vary depending on whether the cells are subjected to uniaxial or biaxial strain [218], or whether cells are aligned parallel or perpendicular to applied uniaxial strain [148]. Another study tested MSCs response to applied shear stress, but is difficult to interpret since neither biological nor experimental microarray replicates were completed [81]. More work is needed to better understand how mechanical conditions impact MSCs signaling.

The cyclic strain due to blood flow that aortic smooth muscle cells experience *in vivo* can be simulated *in vitro* using bioreactors. Aortic smooth muscle cells were exposed to equibiaxial cyclic strain (10%, 1 Hz) for 24 hours on fibronectin-coated silicone using a custom-built bioreactor [267]. Human adult bone marrow-derived mesenchymal stem cells, a cell type proposed for vascular therapies [226] and thought to provide stromal support to endothelial cells *in vivo* [51], were exposed to matched mechanical conditions. Whole human genome microarrays were completed using cDNA samples generated from each treatment group (4 biological replicates/microarray sample; 3 independent experiments/cell type). Strain-responsive transcriptomes in SMCs and MSCs were compared to determine common and cell type-specific mechanosignaling.

4.3 Results

4.3.1 Morphology of cells in response to cyclic strain

MSCs and SMCs seeded on fibronectin-coated silicone were exposed to equibiaxial cyclic strain (10%, 1 Hz) (Figure 14). Neither cell type showed morphological rearrangements

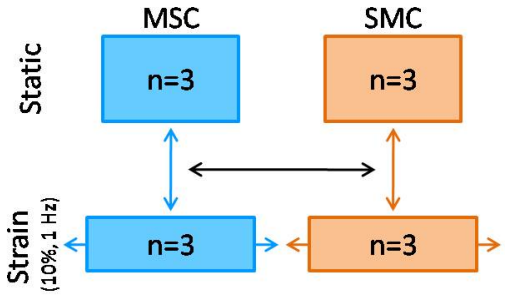


Figure 14: Schematic of cyclic strain microarray experimental design. MSCs and SMCs transcriptomes were compared using whole genome microarray comparison. Paired t-tests for three independent experiments were completed for each cell type (vertical arrows), followed by comparison of strain responses across cell type (horizontal arrow).

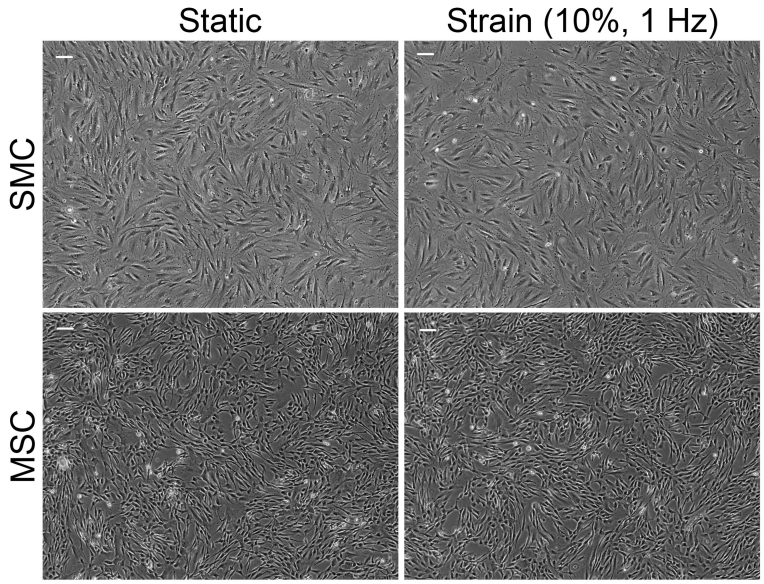


Figure 15: Cell morphology response to equibiaxial cyclic strain. Representative images of MSCs (bottom row) and SMCs (top row) exposed to static culture (left column) or applied strain (10%, 1 Hz) (right column) for 24 hours on fibronectin-coated silicone. Scale bars = 100μm.

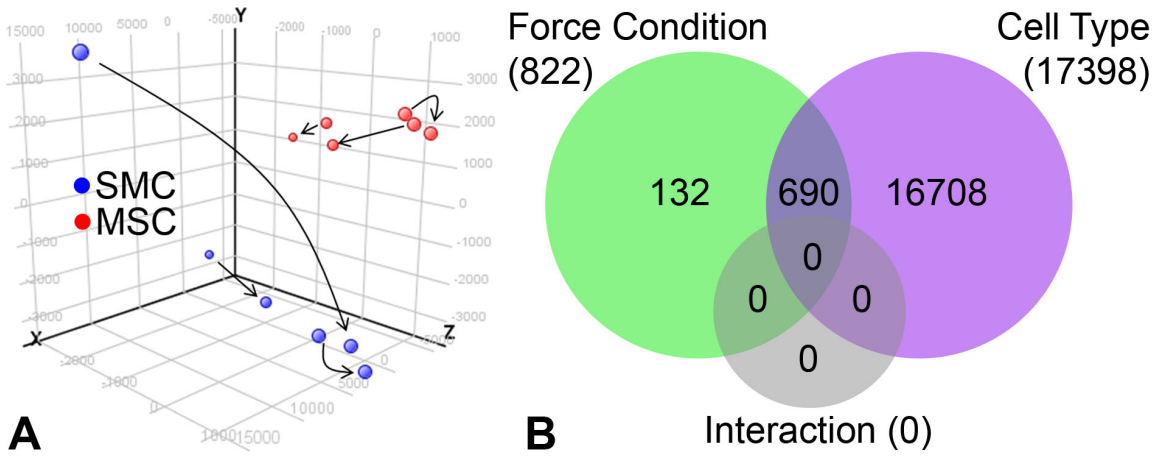


Figure 16: Summary of gene expression differences between sample groups. (A) Principal component analysis, showing cell types group together (MSCs: red, SMCs: blue). Arrows link static to paired strain samples. Principal component 1 (x-axis) separates the cell types. Principal component 3 (z-axis) correlates with SMCs strain vs. static differences. (B) Venn diagram of two-factor ANOVA with Benjamini-Hochberg Multiple Testing Correction results, showing more genes have expression significantly ($p < 0.05$, n=3) dependent on cell-type than force condition.

as assessed by phase images (Figure 15). Density of both cell types increased relative to pre-strain images, suggesting cells proliferate during the duration of applied strain.

4.3.2 Global gene expression responses of MSCs and SMCs to cyclic strain

Pooled MSCs and SMCs samples exposed to either cyclic strain or parallel static culture were assessed using whole human genome microarrays. Principal component analysis indicated that the 12 samples (4 groups; 3 pooled samples/group) segregate primarily according to cell type, via principal component 1, and according to force condition, via principle component 3 (Figure 16A). These large differences in cell type gene expression are corroborated by two-factor ANOVA (Figure 16B). More than 17,000 genes (approximately 50% of the total assessed) have expression significantly (corrected p-value < 0.05, n=3) dependent on cell type. Only 822 genes (approximately 2% of total assessed) have expression significantly dependent on force condition. A minority of these genes (132/822) showed dependence on force condition, but not cell type. No genes were identified with significant interaction effects due to a combination of force and cell type conditions.

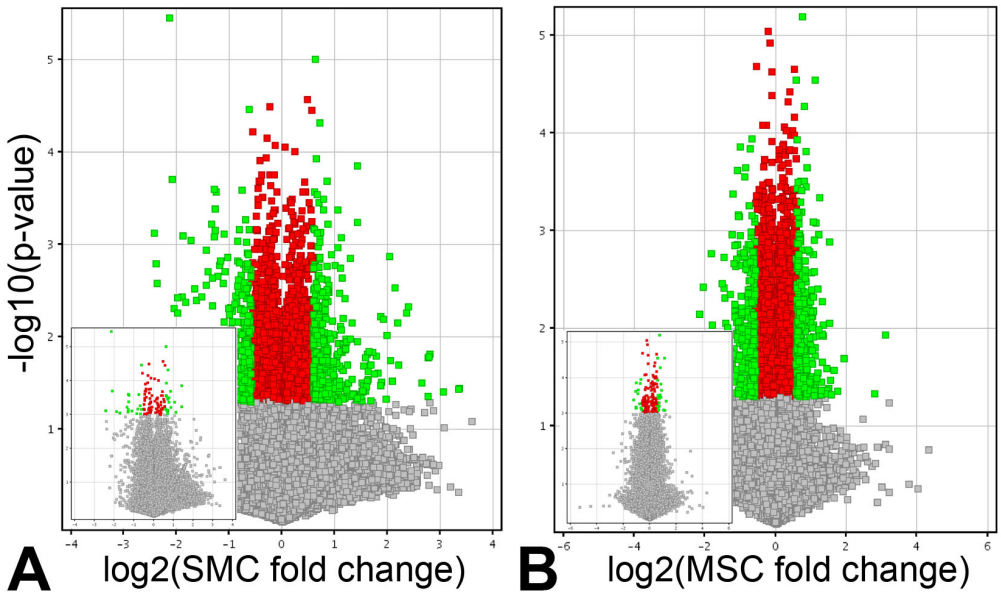


Figure 17: Volcano plots comparing significance and fold-change results in SMCs and MSCs. Genes identified in SMCs (A) and MSCs (B) whose expression alters significantly (colored squares: $p < 0.05$, n=3) by at least 1.5-fold difference (green squares). 36 and 39 genes are identified in MSCs and SMCs, respectively, as highly significantly ($p < 0.001$) strain-responsive (insets). Higher stringency p-value cut-offs were used, since application of MTC resulted in no significantly altered genes.

4.3.3 Significance and fold-change comparisons of MSCs and SMCs cyclic strain response

Strain-responsive genes were also identified using paired t-tests for strain versus static samples. Volcano plots, shown in Figure 17, graphically present the distribution of genes based on fold-change (deviation along the x-axis, left or right of the mid-line) and significance (increasing along the y-axis from the baseline). Genes significantly ($p < 0.05$) upregulated ($|FC| > 1.5$) are shown in green in the upper right quadrant, with those significantly ($p < 0.05$) down-regulated ($|FC| < 1.5$) in green in the upper left quadrant. Spots shown in red indicate genes significantly altered, but below the fold-change sensitivity threshold. Inset figures highlight the distribution of genes under more stringent significance cut-offs ($p < 0.001$). SMCs gene expression was shifted towards lower significance values, compared to MSCs (Figure 17A vs. B) . SMCs fold changes varied $\pm$8-fold relative to paired static controls, with significant genes altering by -4 to +8-fold (Figure 17A). Overall gene expression in MSCs vary $\pm$16-fold, with significant genes occupying a narrower magnitude

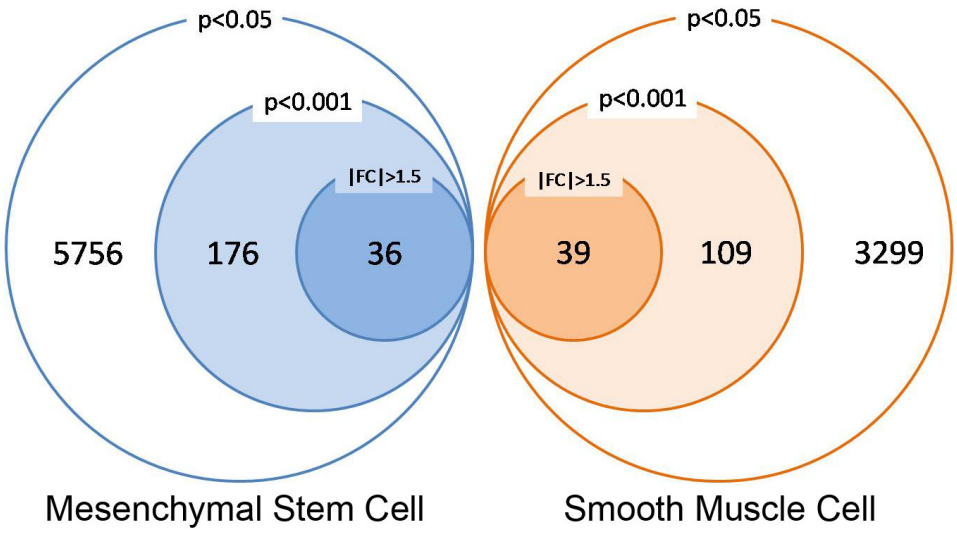


Figure 18: Strain-responsive genes in MSCs and SMCs identified via paired t-tests. Nested circles representing the number of genes with $p < 0.05$ in a paired t-test (no multiple testing correction applied), as shown in the outermost outlined rings; the number of genes with $p < 0.001$, as shown in the lightly shaded rings; and the number of genes with $p < 0.001$ that also change expression levels by at least 1.5-fold, as shown in the darkest shaded center rings. MSCs results are shown in blue (left) or orange (right).

range, approximately $\pm$4-fold (Figure 17B). Significance levels for both cell types ranged four orders of magnitude, from 0.05 to 0.0001.

4.3.4 Paired t-test comparison of MSCs and SMCs strain-response

Figure 18 categorizes the number of genes meeting a range of significance and fold change criteria based on paired t-tests. More genes in MSCs than SMCs are strain-responsive for both low stringency ($p < 0.05$: 5756 vs 3299 genes) and high stringency ($p < 0.001$: 176 vs. 109 genes) p-value thresholds . When multiple testing corrections and fold change cut-offs ($|FC| > 1.5$) are applied, similar numbers of genes are identified in MSCs and SMCs as highly strain-responsive (36 vs 39).

4.3.5 Identification of conserved strain-responsive genes

Genes were defined to be cyclic strain-responsive when expression levels varying by at least 1.5-fold were significantly ($p < 0.05$) different between strain and static samples, determined using at least one of three tests: two-factor ANOVA, paired t-test of SMCs,

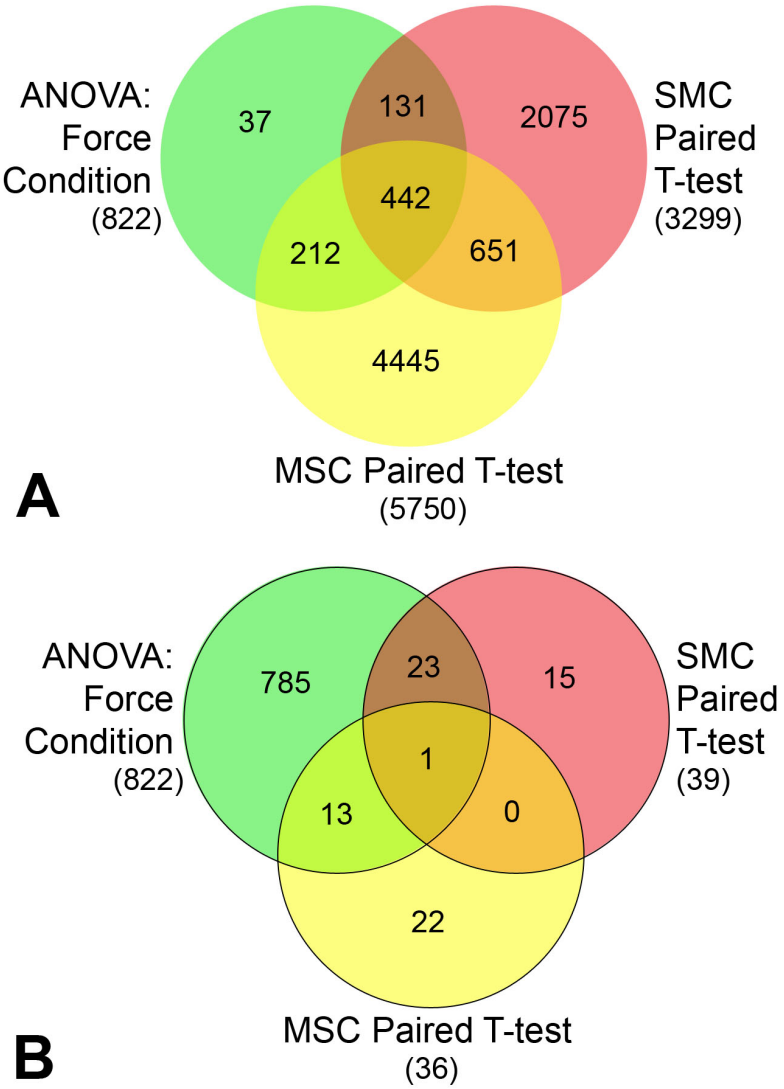


Figure 19: Comparing strain-responsive gene sets identified via two-factor ANOVA or paired t-test. (A) Venn diagram overlays showing significantly different genes (two-factor ANOVA: corrected p-value < 0.05; paired t-tests: p-value < 0.05; n=3). (B) Venn diagram showing high stringency criteria to identify strain-responsive genes. Gene lists were narrowed by correcting p-values for multiple testing using the Benjamini-Hochberg method and increasing p-value ($p < 0.001$, n=3) and paired fold change cut-off ($|FC| < 1.5$) thresholds.

Table 6: Highly significant strain-responsive genes in MSCs. List of genes identified using a paired t-test with $p < 0.001$ and at least 1.5-fold change in expression level.

Gene Symbol	Description	Magnitude Fold Change	GenbankAccession	UniGene
MSC Strain-Responsive Genes (p<0.001 and |FC|>1.5 in paired t-test)				
A_23_P257881		2.078		
A_32_P176174		1.526		
ABCC2	Homo sapiens ATP-binding cassette, sub-family C (CFTR/MRP), member 2 (ABCC2), mRNA [NM_000392]	2.111	NM_000392	Hs.368243
AF086044	Homo sapiens full length insert cDNA clone YX74D05. [AF086044]	-2.213	AF086044	Hs.439682
AIFM2	Homo sapiens apoptosis-inducing factor, mitochondrion-associated, 2 (AIFM2), mRNA [NM_032797]	1.585	NM_032797	Hs.655377
AV707592	AV707592 ADB Homo sapiens cDNA clone ADBAJA03 5', mRNA sequence [AV707592]	-1.502	AV707592	Hs.612413
AW901755	AW901755 QV0-NN1020-170400-192-f12 NN1020 Homo sapiens cDNA, mRNA sequence [AW901755]	-1.745	AW901755	
BIC	Homo sapiens BIC transcript (BIC) on chromosome 21 [NR_001458]	2.336	NR_001458	Hs.662258
C16orf28	Homo sapiens chromosome 16 open reading frame 28 (C16orf28), mRNA [NM_023076]	1.822	NM_023076	Hs.643536
CASP1	Homo sapiens caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase) (CASP1), transcript variant alpha, mRNA [NM_033292]	-1.806	NM_033292	Hs.2490
CCL2	Homo sapiens chemokine (C-C motif) ligand 2 (CCL2), mRNA [NM_002982]	1.646	NM_002982	Hs.303649
CNNM4	Homo sapiens cyclin M4 (CNNM4), mRNA [NM_020184]	2.023	NM_020184	Hs.656229
COL8A2	Homo sapiens collagen, type VIII, alpha 2 (COL8A2), mRNA [NM_005202]	-1.511	NM_005202	Hs.353001
COTL1	Human autonomously replicating sequence (ARS) mRNA. [L08436]	1.592	L08436	Hs.289092
CRY2	Homo sapiens cryptochrome 2 (photolyase-like) (CRY2), mRNA [NM_021117]	1.517	NM_021117	Hs.532491
DCLK2	Homo sapiens doublecortin and CaM kinase-like 2 (DCAMKL2), transcript variant 1, mRNA [NM_001040260]	1.691	NM_001040260	Hs.591683
DDIT4	Homo sapiens DNA-damage-inducible transcript 4 (DDIT4), mRNA [NM_019058]	-1.856	NM_019058	Hs.523012
ENST00000372045	Chordin-like protein 1 precursor (Neuralin-1) (Ventroptin) (Neurogenesin-1). [Source:Uniprot/SWISSPROT;Acc:Q9BU40] [ENST00000372045]	-1.572		Hs.496587
EPHB3	Homo sapiens EPH receptor B3 (EPHB3), mRNA [NM_004443]	-1.636	NM_004443	Hs.2913
FLG	Homo sapiens filaggrin (FLG), mRNA [NM_002016]	-1.537	NM_002016	Hs.654510
FLJ10324	Homo sapiens hypothetical protein FLJ10324 (FLJ10324), mRNA [NM_018059]	-2.153	NM_018059	Hs.667336
GAS1	Homo sapiens growth arrest-specific 1 (GAS1), mRNA [NM_002048]	-1.806	NM_002048	Hs.65029
IL1RAP	Homo sapiens interleukin 1 receptor accessory protein (IL1RAP), transcript variant 1, mRNA [NM_002182]	-1.576	NM_002182	Hs.478673
JAK3	Homo sapiens Janus kinase 3 (a protein tyrosine kinase, leukocyte), mRNA (cDNA clone MGC:39993 IMAGE:5212575), complete cds. [BC028068]	-1.690	BC028068	Hs.515247
MAN1C1	Homo sapiens mannosidase, alpha, class 1C, member 1 (MAN1C1), mRNA [NM_020379]	-1.637	NM_020379	Hs.197043
METTL7A	Homo sapiens methyltransferase like 7A (METTL7A), mRNA [NM_014033]	-1.518	NM_014033	Hs.655369
NDRG4	Homo sapiens NDRG family member 4 (NDRG4), mRNA [NM_022910]	-1.656	NM_022910	Hs.322430
NOSTRIN	Homo sapiens nitric oxide synthase trafficker (NOSTRIN), transcript variant 1, mRNA [NM_052946]	-2.351	NM_052946	Hs.189780
PLEKHK1	Homo sapiens pleckstrin homology domain containing, family K member 1 (PLEKHK1), mRNA [NM_145307]	-2.076	NM_145307	Hs.58559
SEPT6	Homo sapiens septin 6 (SEPT6), transcript variant V, mRNA [NM_145802]	-1.527	NM_145802	Hs.496666
SLC3A2	Homo sapiens solute carrier family 3 (activators of dibasic and neutral amino acid transport), member 2 (SLC3A2), transcript variant 3, mRNA [NM_002394]	1.849	NM_002394	Hs.502769
SOCS2	Homo sapiens suppressor of cytokine signaling 2 (SOCS2), mRNA [NM_003877]	-1.661	NM_003877	Hs.485572
SPANXB2	Homo sapiens SPANX family, member B2 (SPANXB2), mRNA [NM_145664]	2.073	NM_145664	Hs.434105
SQSTM1	Homo sapiens sequestosome 1 (SQSTM1), mRNA [NM_003900]	2.032	NM_003900	Hs.437277
TMEM30B	Homo sapiens transmembrane protein 30B (TMEM30B), mRNA [NM_001017970]	-1.746	NM_001017970	Hs.659339
UNC5B	Homo sapiens unc-5 homolog B (C. elegans) (UNC5B), mRNA [NM_170744]	-1.582	NM_170744	Hs.585457

Table 7: Highly significant strain-responsive genes in SMCs. List of genes identified using a paired t-test with $p < 0.001$ and at least 1.5-fold change in expression level.

Gene Symbol	Description	Magnitude Fold Change	GenbankAccession	UniGene
SMC Strain-Responsive Genes (p<0.001 and |FC|>1.5 in paired t-test)				
A_24_P272910		-1.520		
A_24_P298179		1.596		
A_32_P75141		-1.804		
ABCB6	Homo sapiens ATP-binding cassette, sub-family B (MDR/TAP), member 6 (ABCB6), nuclear gene encoding mitochondrial protein, mRNA [NM_005689]	1.621	NM_005689	Hs.107911
AK091132	Homo sapiens cDNA FLJ33813 fis, clone CTONG2002744. [AK091132]	-1.539	AK091132	Hs.120633
AKR1B10	Homo sapiens aldo-keto reductase family 1, member B10 (aldose reductase) (AKR1B10), mRNA [NM_020299]	5.365	NM_020299	Hs.116724
AL080082	Homo sapiens mRNA; cDNA DKFZp564G1162 (from clone DKFZp564G1162). [AL080082]	-1.560	AL080082	Hs.598166
ARHGAP6	Homo sapiens Rho GTPase activating protein 6 (ARHGAP6), transcript variant 2, mRNA [NM_001174]	-1.578	NM_001174	Hs.435291
C1QTNF6	Homo sapiens C1q and tumor necrosis factor related protein 6 (C1QTNF6), transcript variant 1, mRNA [NM_031910]	-1.635	NM_031910	Hs.22011
C6orf85	Homo sapiens chromosome 6 open reading frame 85, mRNA (cDNA clone IMAGE:3846727), complete cds. [BC022217]	1.811	BC022217	Hs.132340
CAND2	Homo sapiens cullin-associated and neddylation-dissociated 2 (putative) (CAND2), mRNA [NM_012298]	-2.681	NM_012298	Hs.343664
CTSL1	Homo sapiens cathepsin L1 (CTSL1), transcript variant 1, mRNA [NM_001912]	1.545	NM_001912	Hs.418123
CXCL3	Homo sapiens chemokine (C-X-C motif) ligand 3 (CXCL3), mRNA [NM_002090]	2.436	NM_002090	Hs.89690
F2RL2	Homo sapiens coagulation factor II (thrombin) receptor-like 2 (F2RL2), mRNA [NM_004101]	2.421	NM_004101	Hs.42502
FADS1	Homo sapiens fatty acid desaturase 1 (FADS1), mRNA [NM_013402]	1.541	NM_013402	Hs.503546
FLJ20489	Homo sapiens hypothetical protein FLJ20489, mRNA (cDNA clone MGC:26667 IMAGE:4798578), complete cds. [BC026344]	1.692	BC026344	Hs.438867
HMOX1	Homo sapiens heme oxygenase (decycling) 1 (HMOX1), mRNA [NM_002133]	3.308	NM_002133	Hs.517581
HSPB2	Homo sapiens heat shock 27kDa protein 2 (HSPB2), mRNA [NM_001541]		NM_001541	Hs.97013
HTRA3	Homo sapiens HtrA serine peptidase 3 (HTRA3), mRNA [NM_053044]	3.677	NM_053044	Hs.479119
KYNU	Homo sapiens kynureninase (L-kynurenine hydrolase) (KYNU), transcript variant 1, mRNA [NM_003937]	2.458	NM_003937	Hs.470126
KYNU	Homo sapiens kynureninase (L-kynurenine hydrolase) (KYNU), transcript variant 1, mRNA [NM_003937]		NM_003937	Hs.470126
LMCD1	Homo sapiens LIM and cysteine-rich domains 1 (LMCD1), mRNA [NM_014583]		NM_014583	Hs.475353
LOC344887	Homo sapiens mRNA; cDNA DKFZp686B14224 (from clone DKFZp686B14224). [BX640843]	4.273	BX640843	Hs.128803
LOC344887	Homo sapiens mRNA; cDNA DKFZp686B14224 (from clone DKFZp686B14224). [BX640843]	4.429	BX640843	Hs.128803
LTB4DH	Homo sapiens leukotriene B4 12-hydroxydehydrogenase (LTB4DH), mRNA [NM_012212]	2.545	NM_012212	Hs.584864
LXN	Homo sapiens latexin (LXN), mRNA [NM_020169]	-1.714	NM_020169	Hs.478067
NFE2L3	Homo sapiens nuclear factor (erythroid-derived 2)-like 3 (NFE2L3), mRNA [NM_004289]	-1.532	NM_004289	Hs.404741
PLEKHK1	Homo sapiens pleckstrin homology domain containing, family K member 1 (PLEKHK1), mRNA [NM_145307]		NM_145307	Hs.58559
QPRT	Homo sapiens quinolinate phosphoribosyltransferase (nicotinate-nucleotide pyrophosphorylase (carboxylating)) (QPRT), mRNA [NM_014298]	-1.710	NM_014298	Hs.513484
RIT1	Homo sapiens Ras-like without CAAX 1 (RIT1), mRNA [NM_006912]		NM_006912	Hs.491234
SALL2	Homo sapiens sal-like 2 (Drosophila) (SALL2), mRNA [NM_005407]	-1.822	NM_005407	Hs.416358
SELENBP1	Homo sapiens selenium binding protein 1 (SELENBP1), mRNA [NM_003944]	-1.588	NM_003944	Hs.632460
SHROOM3	Homo sapiens shroom family member 3 (SHROOM3), mRNA [NM_020859]	-1.650	NM_020859	Hs.693693
SLC6A4	Homo sapiens solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 (SLC6A4), mRNA [NM_001045]	-1.516	NM_001045	Hs.591192
SLC7A11	Homo sapiens solute carrier family 7, (cationic amino acid transporter, y+ system) member 11 (SLC7A11), mRNA [NM_014331]	2.155	NM_014331	Hs.390594
SOCS2	Homo sapiens suppressor of cytokine signaling 2 (SOCS2), mRNA [NM_003877]	-1.627	NM_003877	Hs.485572
SRXN1	Homo sapiens sulfiredoxin 1 homolog (S. cerevisiae) (SRXN1), mRNA [NM_080725]	2.384	NM_080725	Hs.516830
THC2611140	O96938_CERCA (O96938) Acidic ribosomal protein, partial (16%) [THC2611140]			
THC2615760	Q4S6D5_TETNG (Q4S6D5) Chromosome 9 SCAF14729, whole genome shotgun sequence, partial (3%) [THC2615760]	-2.687		

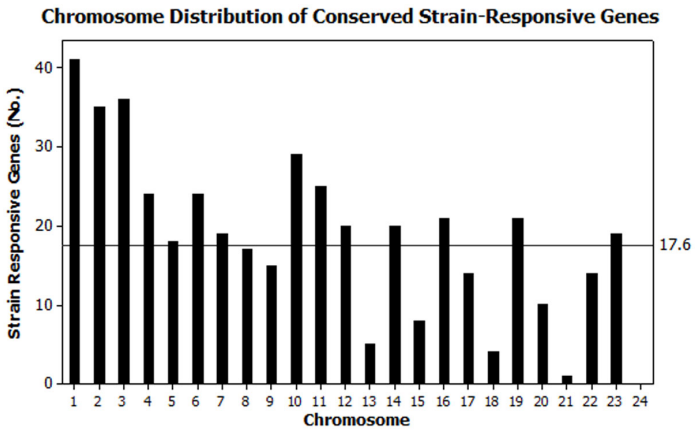


Figure 20: Distribution of conserved, strain-responsive genes according to chromosomal location. 442 genes were identified with significantly ($p < 0.05$, n=3) altered expression levels in response to cyclic strain both two-factor ANOVA and paired t-tests of SMCs and MSCs samples. The histogram above plots the distribution of chromosomal locations for these 442 genes. The reference line indicates the average number of strain-response genes per chromosome (μ=17.6$\pm$11.0). Chromosomes 23 and 24 refer to the X and Y chromosomes, respectively.

or paired t-test of MSCs (Figure 19). Genes that met statistical significance and fold change cut-offs for multiple tests (SMCs; MSCs; ANOVA) were defined as 'conserved' strain-responsive genes. Two-factor ANOVA identified 822 genes with significant ($p < 0.05$) dependence on force condition. Paired t-tests identified approximately 6,000 genes significantly ($p < 0.05$) altered in MSCs and 3,300 genes in SMCs (Figure 19A). When multiple testing corrections were applied and the significance criteria was increased to $p < 0.001$, many fewer genes were identified as strain-responsive: 36 and 39 in MSCs and SMCs, respectively (Figure 19B). Detailed lists of these highly strain-responsive genes are included in Table 6 for MSCs and Table 7 for SMCs. Only one gene, pleckstrein homology domain containing family K member 1 (PLEKHK1), met stringent force-responsive criteria for both cell types. Using the lower p-value threshold ($p < 0.05$), 442 genes are identified as conserved strain-responsive genes by all three statistical tests (Figure 19A). A complete list of these conserved strain-responsive genes is included in the appendix (Table 14).

4.3.6 Chromosomal distribution of strain-responsive genes

To determine whether strain-responsive genes correlated with specific chromosomes, the chromosomal distribution of conserved, significantly strain-responsive genes was determined (Figure 20). This distribution was characterized by a mean (μ=17.6) and standard deviation (σ=11.0) of the number of strain-responsive genes per chromosome. Assuming a normal distribution of strain-responsive genes throughout the genome, the 68% and 95% confidence intervals for number of strain-responsive genes per chromosome are [6.6-28.6] and [0-39.6] respectively. Chromosomes falling outside the 95% confidence level include Chromosome 1 (41 of 442 strain responsive genes). Chromosomes with increased numbers of strain-responsive genes above the 68% confidence interval include 2 (35 genes), 3 (36 genes), and 10 (29 genes). Chromosomes with fewer strain-responsive genes include 13 (5 genes), 18 (4 genes), 21 (1 gene), and Y (0 genes).

4.3.7 Signaling network analysis of conserved strain-responsive genes

The set of 442 conserved strain-responsive genes was analyzed using Ingenuity Pathways Analysis software to identify relationships between these molecules. A signaling network of 730 molecules was generated from the manually-curated database of known gene, protein, and small molecule interactions. These 730 molecules were analyzed for primary subcellular location (Figure 21A) and molecular function (Figure 21B). Genes significantly altered due to strain are found primarily in the cytoplasm (28%), the nucleus (18%) and plasma membrane (14%), and finally the extracellular space (7%). Due to limitations in high-throughput data analysis using IPA, 33% of the molecules in this signaling network were not associated with a particular cellular location.

Molecules in this strain-responsive network were most commonly enzymes (19%); transcription regulators or group molecules (9%); transporters (6%); or kinases, phosphatases, and complex molecules (4%). Only 1% of molecules in this network were growth factors, transmembrane receptors, or endogenous mammalian chemicals. Less than 1% of

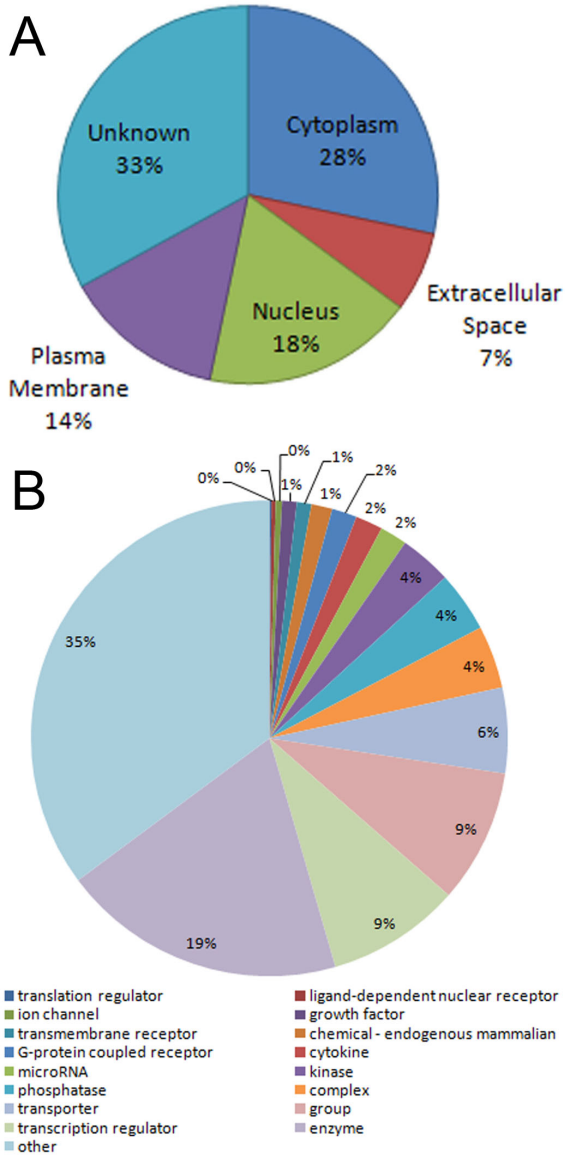


Figure 21: Cellular location and molecular function distribution in strain-responsive signaling network. IPA software analysis of 442 conserved, strain-responsive genes identified a signaling network of 730 genes. (A) Subcellular distribution of molecules from conserved strain-responsive signaling network. (B) Molecular function distribution of molecules in conserved strain-responsive network.

molecules were translation regulators, ligand-dependent nuclear receptors, or ion channels. Similarly to the cellular location analysis, many of these molecules were not associated with a specific molecular type (35%).

4.3.8 Functional and regulatory analysis of strain-responsive genes

DAVID software was used to determine biological functions that correlate to the 442 conserved strain-responsive genes. Clustering analysis with DAVID resulted in 109 functional clusters. Significant ($p < 0.05$) clusters are described in Table 8. Oxidoreductase activity, protein homodimerization, ion homeostasis, and ferritin signaling functions dominated the list of significant clusters. To determine transcriptional regulators involved in the signaling network, conserved strain-responsive genes were analyzed using CARRIE. 24 transcription factors in MSCs and 53 transcription factors in SMCs are predicted to be regulators of strain-response in each cell type (Table 9). Differences in this list of predicted active transcription regulators may be due to fold change difference data for each cell type included in the analysis. 15 transcription factors are predicited to be significantly ($p < 0.001$) involved in mediating cyclic strain response in both cell types.

4.4 Discussion

MSCs and SMCs were exposed to a single force condition, equibiaxial cyclic strain (10%, 1 Hz) for 24 hours on fibronectin-coated silicone, and compared for changes in gene expression. Gene expression varied significantly more with cell type than force condition, as determined using two-factor ANOVA and principal component analysis. Genes in both cell types responded with significant ($p < 0.05, n = 3$), > 1.5-fold magnitude differences, with reduced overall magnitude fold-changes in MSCs. A novel set of 'conserved' strain-responsive genes was defined based on statistical analyses. This set of molecules was found primarily in the cytoplasm and included enzymes and regulators of transcription. Cell functions enriched in this set relate to general cell biology functions including oxidative stress regulation, protein binding, and ion and ferritin homeostasis. Predicted transcriptional regulation of this set of conserved strain-responsive genes included several factors

Table 8: DAVID functional clustering of conserved, strain-responsive genes. DAVID analysis of 442 strain-responsive genes identified with both two-factor ANOVA and paired t-tests identified 12 significant ($p < 0.05$) clusters.

Clustering Group	Associated Function	Median	Associated Genes
2	Oxidoreductase	0.0001	NM_000637, BC035691, NM_153486, NM_001966, BG001037, NM_001353, BC040210, NM_032797, NM_003739, NM_002574, NM_001628, NM_000187, NM_002133, BC014117, NM_030984, NM_000941, NM_080725, NM_020299, NM_002032, NM_000402, NM_018441, NM_015141, NM_002631, NM_032467, NM_004318, NM_032466, NM_005589, NM_021727, NM_012212, NM_000146, NM_001012985, NM_017993, BC035246, NM_002061, NM_002064, NM_002214, NM_031894
1	Oxidoreducatase activity	0.0005	NM_000637, BC035691, NM_153486, NM_001966, BG001037, NM_001353, BC040210, NM_032797, NM_003739, NM_002574, NM_001628, NM_000187, NM_002133, BC014117, NM_030984, NM_000941, NM_080725, NM_020299, NM_002032, NM_000402, NM_018441, NM_015141, NM_002631, NM_032467, NM_004318, NM_032466, NM_005589, NM_021727, NM_012212, NM_002061, NM_001979, NM_000169, NM_014508, NM_021822
3	Protein homodimerization	0.0013	NM_002061, NM_138456, NM_004999, NM_000169, NM_001979, NM_001432, AL050107, NM_002359, NM_004052, NM_020686, NM_005194, NM_004875, NM_152879, NM_021822, M90656, NM_022370, NM_000146, NM_000899,
6	Ion homeostasis	0.0018	NM_000637, BC035691, NM_001353, BC040210, NM_000146, NM_172195, NM_005689, NM_002250, NM_002394, BC014117, NM_030984, NM_002032, NM_001321, NM_004683, NM_152879, NM_000930, M90656, NM_002467, NM_016341, NM_013370, NM_002061, NM_145071, NM_000710, BG001037, NM_001979, NM_002064, NM_000679, NM_002133, NM_053044, NM_000020, NM_031894, NM_004052, NM_005863, NM_004101, NM_022910, NM_000361,
9	Ferritin binding and transport	0.0024	NM_000146, NM_002032, NM_005689, NM_002467, NM_031894, NM_031212, AF495725, NM_001012515, NM_000187, NM_002133, NM_003662, BC014117, NM_030984, NM_000941, NM_032467, NM_004318, NM_032466, NM_021727, NM_002394, NM_002037, NM_002250, NM_031908, NM_004695, BC022217, NM_020184
5	Sulfer metabolic processes	0.0034	NM_002061, NM_000637, BC035691, NM_020686, NM_014905, AF158555, NM_002056, M90656, NM_153486, NM_005746, NM_145791, BC062473, NM_003937, NM_000402, NM_002631, NM_006755, NM_152331, NM_021615
10	Growth regulation	0.0052	NM_013370, NM_145071, NM_004999, NM_004181, NM_000679, NM_053044, NM_002394, NM_020859, NM_006449, AK055915, NM_005010, NM_017734, NM_002037, NM_005863, NM_198859, NM_001321, NM_152879, NM_022910, NM_016341, BX647930, NM_022370, NM_001432
8	Regulation of morphogenesis/cell shape	0.0066	NM_020859, NM_018249, NM_006449, AK055915, NM_005010, NM_017734, NM_002037, NM_203500, AL050107, NM_001432, NM_006521, NM_002359, BX647930
4	Amino acid and lipid metabolism	0.0071	NM_002061, NM_001353, BC040210, NM_001966, NM_002056, NM_003937, NM_001979, NM_005357, NM_000899, NM_003739, NM_000187, NM_003043, NM_152331, NM_031908, NM_020686, BC014117, NM_030984, NM_014905, AF158555, NM_004461, NM_018441, NM_147161, NM_006521, M90656, NM_005589, NM_012212, NM_021727, NM_000169, NM_002214, NM_181523, NM_000475, NM_020299, NM_152879, NM_016341, NM_022060, BE467780, NM_012399, NM_021615, NM_000147
13	Peroxisome	0.0289	NM_001966, NM_003847, NM_001979, NM_018441, NM_016048, NM_152331
11	Metabolic and catabolic processes	0.0430	NM_001012515, NM_002061, NM_153486, NM_000637, BC035691, NM_003937, NM_002133, NM_152331, NM_005746, NM_145791, BC062473, NM_000402, NM_002631, NM_006755, M90656, NM_002056, NM_000169, NM_000679, NM_001032289, NM_021615, NM_001628, NM_000158, NM_031908, NM_002394, NM_005398, NM_000147, NM_033500, NM_019593, NM_015141, NM_014580, NM_000022, NM_005589, NM_199040, NM_004695, NM_005357
15	Protein kinase activity	0.0444	NM_031908, NM_201444, NM_145071, BE467780, NM_006705, NM_152879, NM_001432, NM_016341, NM_002061, NM_022550, NM_020185, NM_000169, NM_004683, NM_000679, NM_002386, NM_199040, NM_002133, NM_181523

Table 9: Transcription regulatory networks predicted to mediate MSCs and SMCs response to cyclic strain. CARRIE analysis was used to analyze transcription networks regulating the set of 442 conserved, strain-responsive genes. Transcription factors were identified as significant ($p < 0.001$) in either cell type based on paired fold change levels in each cell type.

CARRIE Regulatory Relationship Analysis		
Transcription Factor	**SMC P-value**	**MSC P-value**
POU3F2	2.35E-10	--
upstream stimulating factor	6.71E-10	--
signal transducer and activator of transcription 5b	7.38E-09	--
HFH-4	2.49E-08	--
NKX6-1	1.42E-07	--
complex of Lmo2 bound to Tal-1, E2A proteins, and GATA-1, half-site 1	3.46E-07	--
LIM homeobox transcription factor 3	4.28E-07	--
fork head box J 2	5.55E-07	--
Tal-1alpha/E47 heterodimer	5.64E-07	--
signal transducer and activator of transcription 5a	1.17E-06	3.59E-04
HFH-3 (HNF3/fork head homolog 3)	1.41E-06	--
POU3F2	1.52E-06	--
POU1F1	2.30E-06	--
TCF11/KCR-F1/Nrf1 homodimers	2.68E-06	--
HNF-3	4.05E-06	--
activator protein 4	8.66E-06	6.00E-04
modulator recognition factor 2	1.58E-05	--
AP-1 binding site	1.65E-05	--
Hand1/E47 heterodimer	2.16E-05	--
HNF-6	2.65E-05	--
myoblast determining factor	4.10E-05	--
TEF	4.15E-05	5.17E-04
58 KDA repressor protein	5.58E-05	2.94E-04
HNF-1	6.58E-05	7.59E-04
activator protein 1	6.81E-05	--
fork head box J 2	9.23E-05	--
POU-factor Tst-1/Oct-6	9.55E-05	--
Meis-1 (myeloid ecotropic viral integration site 1)	9.74E-05	2.08E-04
Fork head RElated ACtivator-7	1.17E-04	1.00E-04
Fork head RElated ACtivator-4	1.24E-04	--
Pit-1	1.25E-04	1.37E-04
SRF	1.66E-04	1.09E-06
fork head box O3	1.74E-04	1.88E-04
DBP	1.86E-04	--
fork head box D3	1.94E-04	--
fetal Alz-50 clone 1	1.96E-04	7.93E-05
CCAAT/enhancer binding factor	2.58E-04	--
USF binding site	3.88E-04	--
FOX	4.45E-04	--
octamer factor 1	4.54E-04	--
HNF-3alpha	4.90E-04	--
Hepatic nuclear factor 1	5.02E-04	4.38E-07
NK related homeobox factor 6-2	6.11E-04	2.94E-04
C/EBPgamma	6.13E-04	--
Meis-1b/HOXA9 heterodimeric binding	6.48E-04	4.70E-07
myogenic enhancer factor 2	6.62E-04	4.42E-05
TATA binding protein	8.22E-04	--
TCF11/MafG heterodimers	8.66E-04	--
zinc finger with interaction domain	9.23E-04	--
AML	9.31E-04	--
E12	9.59E-04	--
AP-1	9.66E-04	--
HEB	9.93E-04	--
hepatic nuclear factor 1	--	7.50E-07
IRF1	--	1.88E-05
POU3F2	--	5.18E-05
Retroviral TATA box	--	1.34E-04
Crx	--	2.94E-04
interferon regulatory factor 1	--	3.72E-04
myogenic MADS factor MEF-2	--	3.83E-04
Fork head RElated ACtivator-3	--	4.07E-04
FXR inverted repeat 1	--	7.24E-04

in both SMCs and MSCs and others specific to one cell type, mimicking the conserved and cell type-specific components of the gene response.

Due to the expense of microarray analysis, only one cyclic strain condition was assessed per cell type. Future work is needed to describe protein-level changes. Thus, the set of identified strain-responsive molecules is biased towards those whose response occurs at the mRNA level. Future studies may identify other molecules as strain-sensitive that are altered post-transcriptionally. To generate sufficient genes in the intersection defined as 'conserved' strain-responsive, multiple testing corrections were not applied to all paired t-test analyses. Efforts to sort data based on multiple different criteria (with or without MTC, with or without fold change cut-offs, statistical significance in multiple tests, etc.) were used as a means to triangulate on the conserved force-responsive molecules.

Neither MSCs nor SMCs showed obvious cellular rearrangements following cyclic strain on fibronectin-coated silicone. The morphological similarities between samples exposed to cyclic strain or parallel static culture belie the marked differences in gene expression occurring in both cell types. Transcriptome responses in each cell type were initially assessed with global measures, PCA and two-factor ANOVA. The separation of sample groups (cell type; force condition) along defined principal component axes indicates cellular behavior can be described based on mathematical descriptions. Three principal components were required in order to separate static versus strain samples, suggesting that other factors, including cell type and possibly biochemical media type, dominate signaling differences of principal component 1 and 2. Follow up work could test whether the axes defined in GeneSpring's PCA correlate with altered expression of a particular subset of genes.

Two types of statistical tests were used to identify individual strain-responsive molecules in either or both cell types: two-factor ANOVA and paired t-tests. The paired t-tests were necessary due to inherent experimental variability. Paired data was not accounted for in the ANOVA, leading to two differences from paired t-tests: (1) some genes were significantly only in paired t-tests because pairing could detect a trend obscured by noisy data and (2) some genes were significantly force-dependent only in the ANOVA because subtle cyclic strain vs. static differences required more replicates (e..g, n=6 vs. n=3) to detect.

ANOVA highlighted the strong cell type-dependence of gene expression, with approximately 50% of genes dependent significantly on cell type versus 2% dependent on force condition. Genes significantly altered in SMCs ($p < 0.05$ or $p < 0.0001$) had larger average magnitude fold changes than genes significantly altered in MSCs. It is not possible to determine based on this data whether the highly significant ($p < 0.001$) gene changes observed in MSCs at low fold change magnitudes ($|FC| < 1.5$) are functionally important. One possibility is that lower abundance transcripts in stem cells may be able to trigger functionally important events related to differentiation, reasonable given the effects of low abundance pluripotency factors such as Oct4 [312]. Analysis of nested sets of significant and fold-change cut-off genes indicate similar numbers of genes are identified as most strain-responsive (corrected p-value< 0.001 and $|FC| > 1.5$) in both cell types. With these most stringent criteria for strain-sensitivity, only one molecule appears in both MSCs and SMCs sets. The fact that many more genes are identified with slightly relaxed criteria ($p < 0.05$ in all three statistical tests) suggests that specific molecules may be regulated at different precision levels between cell types.

Pleckstrein homology domain containing family K member 1 (PLEKHK1) is the only gene that met stringent force-responsive criteria (corrected p-value < 0.001) for both cell types. PLEKHK1, also known as rhotekin 2 (RTKN2), is an intracellular plasma membrane-associated molecule conserved across multiple species and involved in hematopoiesis, cell proliferation, and signal transduction [49]. Very little is known about PLEKHK1 and there are no reports of force-sensitivity of this molecule. However, association of PLEKHK1 with the force-associated RhoA pathway suggests it may be strain-sensitive [5]. The conserved Rho binding domain of PLEKHK1 binds the activated, GTP-bound form of the small GTPase RhoA. RhoA binds ROCK, inhibiting myosin phosphorylation, affecting force sensing and force generation.

Data published by other groups has shown regions of genomic DNA can be sensitive to applied mechanical forces [25]. The heterogeneous distribution pattern observed in this case suggests that a subset of chromosomes (e.g., Chromosome 1) may be predisposed to alter gene regulation in response to cyclic strain. Other chromosomes may be more

resistant to mechanically-induced transcription changes.

No clear bias between cytoplasmic, nuclear, or plasma membrane-associated components was observed in the IPA-generated conserved strain-responsive signaling network. The low fraction of extracellular space molecules identified may result from a bias due to gene expression or because mechanosensitive regulation of extracellular-associated molecules occurs at the protein level. The prevalence of enzymatic functions in this signaling network suggests conserved strain-responses alter the potential signaling reactions that can occur within cells exposed to cyclic strain. Transcription regulator involvement in the conserved strain response suggests a feed-forward regulatory loop may exist, translating gene expression changes into subsequent changes in transcription regulation.

The functions identified using DAVID analysis are associated with physiologic function of multiple cell types, rather than specialized functions of differentiated cell types. This is consistent with the theory that mechanosensing is an inherent function of which all cells are capable, as well as one that affects fundamental cell maintenance processes [111, 296]. Analysis with CARRIE to predict transcription factors that regulate the observed response to cyclic strain highlights 15 factors likely to be involved in controlling cell signaling in both cell types. This set of common transcription factors includes examples of known mechanical strain-sensitive transcription factors like serum response factor (SRF) [306].

4.5 Conclusions

This work identifies a set of genes that may mediate cellular response to applied cyclic strain in multiple cell types. This work includes those known to be strain-responsive (e.g., SRF), as well as novel genes (e.g., PLEKHK1). The wide distribution of strain-sensitive molecules in the cell, representation among essential molecule types like enzymes, and association with necessary cell functions like oxidoreductase activity collectively highlight the importance of mechanical cues in controlling cell signaling. Future studies may investigate whether these strain-responses are also conserved across other cell types. Accounting for differences in MSCs vs. SMCs strain-response may enable more controlled use of MSCs in a vascular cell-based therapy.

4.6 Materials and Methods

Supplies Cells and culture media were purchased from Lonza. PCR arrays and associated materials were purchased from SA Biosciences. Standard qPCR reagents were purchased from Qiagen (RNA isolation), Invitrogen (cDNA synthesis), and ABI (qPCR mastermix).

Cell culture of MSCs & SMCs Human adult bone marrow-derived mesenchymal stem cells and aortic smooth muscle cells were cultured according to manufacturer's recommendations (Lonza). MSCs were expanded to Passage 6 and characterized for expression of protein surface markers and differentiation potential along osteogenic, chondrogenic, and adipogenic lineages prior to experimental use. SMCs expanded to Passage 3 were used for experiments.

Applied strain Equibiaxial cyclic strain was applied using a custom-built device [267]. Briefly, cells were seeded on etched, human plasma fibronectin-coated silicone at 10,000 cells/cm^2, calculated using a Coulter Counter Multisizer 3 (Beckman Coulter). For each membrane holder chamber (MHC), cells were allowed to attach in 2 ml media for four hours at 37·C, prior to addition of media up to 25 ml final volume and static preconditioning culture on the silicone substrate for 48 hours total. Samples were subsequently exposed to defined applied strain (10%, 1 Hz) or parallel static culture for $\leq$24 hours. To assess cell morphology, phase images of samples were taken using an Axiovert microscope (Zeiss) immediately prior to and following exposure to mechanical force.

Microarray sample preparation To minimize noise due to biological and experimental variability, cell lysates were pooled from four independent samples per static or applied strain replicate. Experiments were completed in triplicate. RNA was isolated according to manufacturer's protocols using an RNeasy Isolation Kit (Qiagen). All samples passed two levels of quality control: first, the concentration, $A_{\frac{260}{280}}$, and $A_{\frac{260}{230}}$ were measured using a Nanodrop (Thermo Scientific) and second, the RNA integrity number (RIN) was determined using a Bioanalyzer (Agilent). cDNA synthesized from high quality RNA samples was labeled for one-color detection and run on a whole human genome 60-mer microarray (Agilent), four arrays per slide. Microarray images were captured using Feature Extraction

software and passed manufacturer-recommended quality control metrics for image uniformity.

Microarray data analysis Feature Extraction data was imported into Gene Spring 10.0 for normalization and statistical assessment. 12 of 12 arrays passed quality control metrics within GeneSpring, enabling three replicates per group to be analyzed. Genes were filtered to ensure present or marginal expression levels in at least one sample. ANOVA with Benjamini-Hochberg multiple testing correction of all sample groups was used to determine whether gene expression depended significantly on cell type or force condition. T-tests with paired static and strain samples per experiment were used to identify genes significantly altered in either SMCs or MSCs. When multiple testing corrections applied to paired t-tests resulted in few to no genes identified, increased significance cut-offs (p=0.001 vs. p=0.05) were used instead. Conserved strain-responsive genes were defined as those meeting three criteria: two-way ANOVA significant dependence on applied force ($p < 0.05$), SMCs paired t-test significant difference between static and applied strain groups ($p < 0.05$), and MSCs paired t-test significant differences ($p < 0.05$).

Functional, regulatory, and subcellular location analysis of strain-responsive genes was completed using Ingenuity Pathways Analysis (Ingenuity), the Database for Annotation, Visualization and Integrated Discovery (DAVID) 2008 [107, 64], and the Computational Ascertainment of Regulatory Relationships (Inferred from Expression) (CARRIE) software [93, 94]. For IPA analysis, GenBank Accession Numbers for the set of conserved force-responsive molecules were uploaded as a data set and analyzed for core analysis using direct and indirect relationships, endogenous chemicals, and up to 25 networks per analysis, each with up to 35 molecules. Descriptions for each molecule associated with the resulting 25 networks of direct and indirect interactions were exported from IPA into MS Excel and sorted according to molecular function or subcellular location. GenBank accession numbers for conserved force-responsive probes were uploaded to the DAVID interface as the gene list and compared to the Homo sapiens background gene list. Functional annotation clustering was performed via DAVID version 6.7b and results exported to MS Excel for table formatting. Both IPA and DAVID analysis relied only on GenBank Accession

numbers. For prediction of transcriptional regulators, both GenBank Accession numbers, as well as fold change and p-values, were uploaded for each cell type. Pre-processed array data in this format were uploaded and analyzed using the TRANSFAC Human matrix list and HG-U133 promoter list. Transcription factors were defined as significant if the frequency of significant sites in random promoters was $< leq$0.001 and the p-value for binding site overabundance in one promoter was $\geq$0.01. Finally, chromosomal location analysis was completed by sorting data output from GeneSpring for the conserved set of force-responsive probes.

Standard qPCR assessment Individual genes were assessed using standard qPCR. RNA was isolated from kinetic experiments and quantified as above. cDNA was synthesized using a FirstStrand III SuperScript Kit (Invitrogen) and prepared for qPCR with custom designed primers (Primer Express 3 software; Invitrogen custom primer synthesis; ABI SYBR mastermix). qPCR samples were run on a StepOne Plus machine (ABI) and baseline-subtracted C_t analyzed in Excel (Microsoft). All data were converted to molar concentrations using a standard curve and normalized to Gapdh expression. Two fold-changes were calculated: a strain response (the ratio of strain/static relative expression) and a cell type response (ratio of MSCs/SMCs expression under respective maintenance conditions). A 1.5-fold change threshold was used to identify strain-responsive genes. Fold change in gene expression calculated using microarrays versus qPCR were compared.

Statistical analysis Microarray data were analyzed with two-factor ANOVA or paired t-test. Functional significance was determined using statistical methods inherent in IPA, DAVID, or CARRIE, respectively. qPCR data was analyzed in MS Excel with two-tailed paired t-tests. Experimental design was employed to minimize the effect of biological variability (i.e., 4 pooled samples per microarray) and randomize the effect of experimental variability (n$\geq$3 independent experiments/comparison). Significance cut-offs, defined explicitly throughout the text, were either $p < 0.05$ for low-stringency or $p < 0.001$ for high-stringency conditions.

4.7 Acknowledgements

We are grateful to Leonard Anderson, Guoshen Wang, and Michelle Leander at the Morehouse School of Medicine core facility for help running microarrays and preliminary microarray analysis.

CHAPTER V

MESENCHYMAL STEM CELLS RESPOND TO SHEAR STRESS WITH REDUCED INFLAMMATORY SIGNALING

5.1 Abstract

MSCs may contribute to an endothelial therapy via differentiation or their ability to modulate cell behavior via paracrine signaling. Inflammation and immune-related signaling are early onset, functionally-important indicators of the vascular response to shear stress, yet the ability of MSCs to signal in a site-appropriate manner has not been quantified. The objective of this study was to determine the signaling response of MSCs to physiologically-relevant vascular shear stress, in comparison with that of ECs. MSCs and ECs were exposed to two different shear stress magnitudes (5 or 15 dyn/cm^2 or parallel static control) and durations (0, 2, 6, 12, or 24 hours) using a parallel plate shear system. RNA isolated from all samples was assessed using quantitative RT-PCR for expression of genes characteristic of ECs differentiation or ECs inflammatory response to shear stress. MSCs response to shear stress was similar to ECs for Cox-2, Hmox-1, and vWF. MSCs expression was undetectable or unresponsive to shear stress for eNos, Klf2, and VE-Cad, in contrast with shear-sensitivity in ECs. MSCs and ECs response to shear stress altered in opposite directions for Pecam-1 and Mcp-1. These results indicate that shear stress triggers an immune and inflammatory response in both ECs and MSCs. In addition, this data demonstrates that shear stress alone is not sufficient to differentiate MSCs towards ECs within 48 hours. This work highlights genes with mechanosensitivity conserved across cell type, meriting future investigation into the functional importance of this conserved immune/inflammatory response and into the mechanism(s) controlling the shear-response in both cell types. This work shows MSCs may reduce inflammatory and immune signaling in repsonse to vascular-relevant shear stress, without necessarily differentiating along an endothelial lineage.

5.2 Background

Cell-based therapies may improve on current clinical options by employing biological mechanisms not yet possible to engineer synthetically. Mesenchymal stem cells, one potential cell source, are an adult multipotent mesenchymal cell type classically defined as bone marrow-derived and capable of differentiating towards orthopedic and adipogenic lineages. Recent studies have derived MSCs-like cells from a wide variety of tissues and demonstrated their differentiation potential towards a broader range of cell types. Studies of MSCs for vascular applications have shown MSCs can adopt traits of differentiated vascular cells; reduce inflammatory damage and immune response and promote growth via paracrine factors; and are phenotypically similar to pericytes, an in vivo cell type supporting the vasculature. The potential of MSCs to mimic vascular cell response to physical forces remains poorly characterized though. The objective of this study was to determine the response of mesenchymal stem cells to fluid shear stress, a mechanical cue known to regulate immune and inflammatory signaling in endothelial cells.

Immunity and inflammation are involved in angiogenesis, atherosclerosis, tumor progression, and diabetes, among other functional markers of health and disease [31]. Inflammation is the process by which the body responds to injury (physical, chemical, microbial, etc.) and attempts to remove the irritant and enable tissue repair [193]. Inflammatory cues trigger an immune response, a process through which foreign and disease components are identified and killed [169]. Depending on the initial trigger, the inflammation and immune response may resolve normally or may persist as a chronic condition. Endothelial cells play a critical role regulating the chemoattractive and adhesive environment of the vessel lumen, and thereby the inflammatory and immune activity at the vessel wall [175]. Cytokines, chemokines, adhesive molecules, and oxidative stress regulators signal as part of ECs regulation of immune and inflammatory responses [175, 169, 215]. Several of these molecules are known to be responsive to blood flow, as summarized in Table 10. While these signaling molecules each contribute to inflammation and immune activation, they can also interact with one another (Figure 29).

Table 10: Genes involved in endothelial cell regulation of immune and inflammatory responses. Gene names, and their synonyms, are listed in terms of functional category relevant to these studies, subcellular location, molecular function type, biological function, and known gene expression response to applied shear stress in endothelial cells.

Gene Name (Symbol)	Category	Cellular Location	Type	Function	EC Gene Response to Shear Stress
Prostaglandin-endoperoxide synthase 2 (Cox2)	Inflammation; Immune	Cytoplasm	Enzyme	anti-inflammatory	increases
Nitric oxide synthase 3 (endothelial cell) (eNos, Nos3)	Inflammation; Immune	Cytoplasm	Enzyme	NO production; vasorelaxant, decreases oxidative stress	increases
Heme oxygenase (decycling) 1 (Hmox1)	Inflammation; Immune	Cytoplasm	Enzyme	catabolizes heme; anti-oxidant, anti-inflammatory	increases
Kruppel-like factor 2 (lung) (Klf2)	Inflammation; Immune	Nucleus	Transcription Regulator	anti-inflammatory; reduces T cell attachment and rolling	increases
Chemokine (C-C motif) ligand 2 (Mcp1, Ccl2)	Inflammation; Immune	Extracellular Space	Cytokine	monocyte chemoattractant	decreases
Platelet/endothelial cell adhesion molecule (Pecam1)	EC Differentiation; Immune	Plasma Membrane	Other	EC homotypic binding; binding to leukocytes during diapedesis	increases
Cadherin 5, type 2 (vascular endothelium) (VE-Cad, Cdh5)	EC Differentiation; Immune	Plasma Membrane	Other	EC homotypic binding at adherens junctions; decreases EC permeability	increases
von Willebrand factor (vWF)	EC Differentiation; Inflammation	Extracellular Space	Other	clotting cascade; binds platelets	Not reported

Several options have been proposed for incorporating MSCs in a vascular therapy. For prefabricated vascular grafts, MSCs may be seeded on the inside of a synthetic or natural polymer tube, mimicking endothelialization [294]. For cardiac applications, in which local vascularization may be desired, MSCs may also be presented in a homogenous gel to be used as a patch on the injured area [262]. Direct delivery of MSCs is possible through intravascular (systemic) or intramuscular or endocardial (local) injection [229]. Cells used may vary in preparation, ranging from fresh bone marrow preparations to preconditioned, differentiated MSCs-derived cells. The therapy may employ MSCs as a solo cell therapeutic or in combination with other therapeutic components [229]. In all cases, MSCs intended to line the lumen of a vessel will be subjected to shear stress.

Both mesenchymal stem cells and endothelial cells arise from the mesoderm. Mesenchymal stem cells *in vivo* are associated with the perivascular niche [51, 29] Undifferentiated MSCs express markers functionally important in ECs, such as VEGF [332]. Animal and human clinical trials of MSCs-based cardiovascular therapies indicate these cells may adopt traits of vascular cells upon implantation [80]. Genetic engineering techniques for

Tie2, Flk1, Ang, Vegf, and eNos have been used to track and/or promote endothelial-like differentiation. Both biochemical and mechanical cues have been used to enhance the endothelial phenotype of MSCs *in vitro* [118, 66]. Soluble (VEGF, IGF, EGF, bFGF, hydrocortisone, ascorbic acid, heparin) and insoluble (extracellular matrix) biochemical cues can increase expression of endothelial gene and protein markers and improve functional assessments such as formation of tubes on Matrigel [332, 168, 167]. Shear stress has been shown to upregulate and sustain expression of endothelial-related markers in the presence of biochemical stimuli, but may not be sufficient to trigger endothelial differentiation alone [15, 8]. Gene and protein expression levels are frequently employed metrics to assess differentiation. For the majority of these both *in vivo* and *in vitro* studies, expression levels of PECAM-1, an early marker, and VE-Cad and vWF, later markers, were used to infer endothelial differentiation.

MSCs may contribute to vascular health through paracrine actions, rather than direct differentiation [12]. MSCs secreted factors can promote cell proliferation and inhibit cell death. MSCs-secreted growth factors also promote angiogenesis. Secretion of proteases by MSCs enables chemical composition and mechanical property remodeling of the tissue. Presence of MSCs in a vascular injury can affect cell migration and recruit reparative and replacement cell types to the area. MSCs unique cytokine and HLA expression profiles enable them to modulate and suppress inflammation and immune reactions in the surrounding tissue.

The responses of MSCs to applied shear stress have been investigated primarily for osteogenic and vasculogenic mechanical regimens. Shear stress at osteogenic-relevant levels has been shown to promote osteogenic differentiation [327, 132, 271, 255]. Computational models to predict the effects of compression and fluid flow have also been developed to predict MSCs response to flow [327, 129]. Several groups have investigated shear stress as a method to enhance endothelial differentiation of MSCs and related cell types (e.g., amniotic fluid- or adipose-derived stem cells) [8, 15]. These data conflict regarding the effect of shear stress as a sufficient cue to differentiate MSCs towards endothelial cells within 48 hours. *In vivo*, MSCs are likely exposed to low levels of shear stress in the bone

marrow environment. MSCs-like cells have also been isolated from other locations with shear stress (amniotic fluid; human umbilical cord) [282]. Few studies have been done to analyze shear stress-sensitive cell signaling, independent of differentiation markers.

Evidence to date suggests MSCs are promising options for vascular therapies and potentially endothelial cell substitutes. Shear stress alters MSCs signaling and behavior as a function of shear stress parameters (magnitude, duration, duty cycle, and ramp) and interaction with biochemical cues. Control of immune and inflammatory signaling is an important component of physiological response of ECs to shear stress. However, parallel assessments have not been reported describing whether MSCs can mimic this response. In this study, ECs and MSCs are exposed to varied magnitude and duration steady laminar shear stress and assessed for changes in a panel of 8 immune and inflammation markers. Shear stress promotes an anti-inflammatory, immunosuppressive state in MSCs, without evidence of endothelial differentiation.

5.3 Results

5.3.1 Cell shape and number in response to shear stress

Cells were subjected to steady laminar shear stress (5 or 15 dyn/cm^2) or parallel static culture in their respective culture media. Samples were visualized with phase microscopy and RNA harvested for gene expression assessment after 0, 6, 12, 24, or 48 hours. ECs exposed to 15 dyn/cm^2 shear stress elongate and align parallel to the direction of shear within 48 hours. Small areas of local cell alignment are visible within 12 hours of applied shear, as shown in Figure 22A. ECs exposed to 5 dyn/cm^2 shear stress do not markedly elongate or align parallel to the direction of applied shear. Qualitatively, cells appear to align perpendicular to the direction of applied shear stress. Cell number increased markedly in static samples, but not shear samples, during the 48 hour culture period. Cell density after 48 hours applied shear stress of either 5 or 15 dyn/cm^2 resulted in lower cell density than parallel static samples.

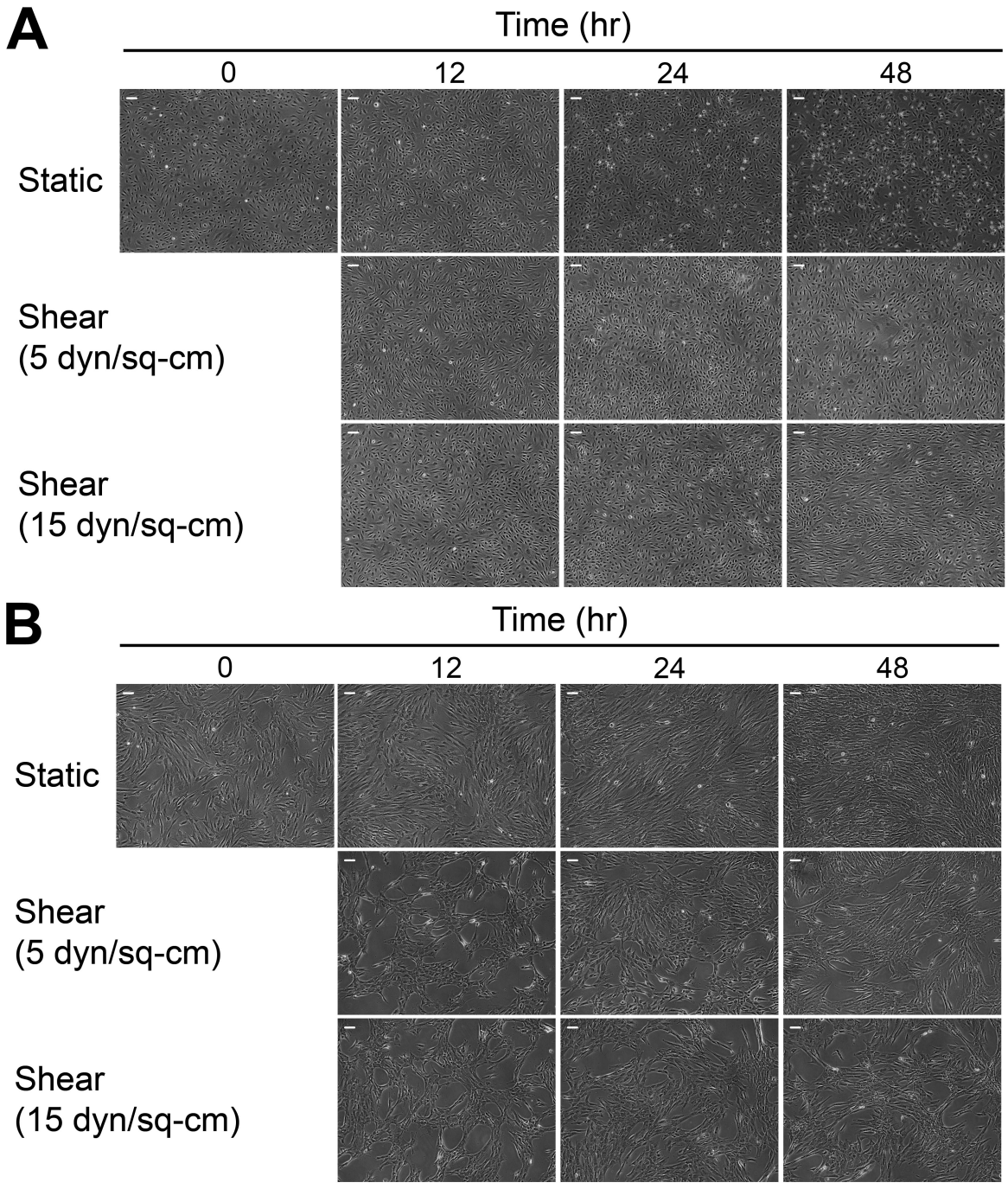


Figure 22: Phase morphology of ECs and MSCs in response to static or applied shear stress culture. ECs (A) and MSCs (B) after static culture (A & B, top row), 5 dyn/cm^2 shear stress (A & B, middle row), or 15 dyn/cm^2 (A & B, bottom row) applied shear stress. Scale bars = 100μm.

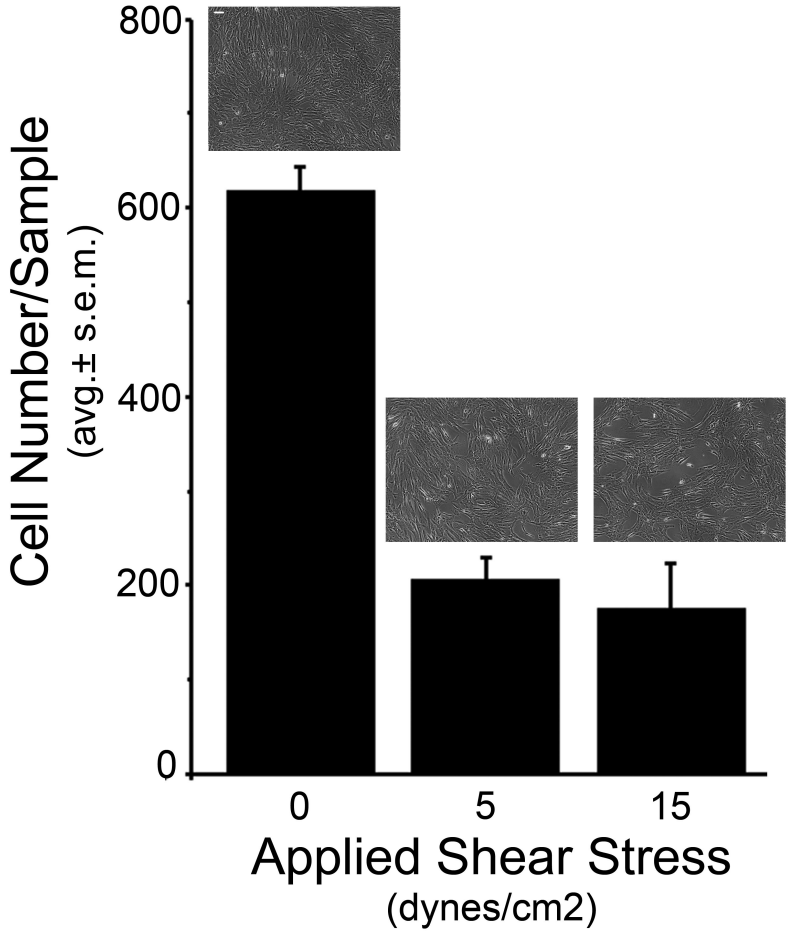


Figure 23: Quantification of cell number and viability in MSCs, using ViCell. Cell number decreases significantly in response to applied shear stress, with no significant differences between shear magnitudes of 5 and 15 dyn/cm^2. Viability does not change significantly (p=0.234, n=3) between groups.)

MSCs cultured on Type I Collagen-coated glass slides are spindle-shaped cells occupying more surface area than ECs. Applied shear stress up to 48 hours does not promote a cobblestone morphology in MSCs. Similar to ECs, MSCs cell density increases markedly in static samples, but not shear samples, during 48 hours. Cell number significantly ($p \leq 0.001$, n=3) decreased in response to shear stress, although viability did not (p=0.234, n=3), as shown in Figure 23. Inhomogeneous cell density of MSCs appears within 12 hours of applied shear (5 or 15 dyn/cm^2), relative to the same samples immediately prior to shear and to time-matched static control samples. These gaps and clusters persist in shear samples throughout 48 hours of applied shear stress. Gaps are larger and more rounded in samples exposed to 15 dyn/cm^2 compared to 5 dyn/cm^2. Alignment of MSCs parallel to the direction of applied shear stress is present only in local areas and after at least 24 hours applied shear stress.

5.3.2 Overall gene expression comparison

Expression of eight genes characteristic of endothelial cells and immune/inflammatory response were quantified using real time-PCR. MSCs had $\leq 10^3$ lower expression for vWF, eNos, Pecam-1, and VE-Cad, with the latter three indistinguishable from no template qPCR controls. Cox2, Hmox1, Klf2, and Mcp1 were expressed at similar magnitudes in MSCs and ECs. On average, shear stress resulted in significant differences in gene expression in ECs earlier than MSCs. ECs also had larger average fold change gene expression levels due to applied shear stress.

5.3.3 Shear response of endothelial differentiation genes

qPCR results from immune and inflammatory genes also characteristic of endothelial differentiation are shown in Figure 24. In ECs, Pecam-1 expression steadily and significantly ($p \leq 0.05$, n=3-4) increases from 6 to 48 hours of applied shear stress (5 or 15 dyn/cm^2). VE-Cad expression increased significantly after 24 hours (5 dyn/cm^2) and 48 hours (5 and 15 dyn/cm^2). vWF expression increased slightly throughout the duration of applied shear, but was significant only after 6 hours of shear stress at 15 dyn/cm^2. Fold change

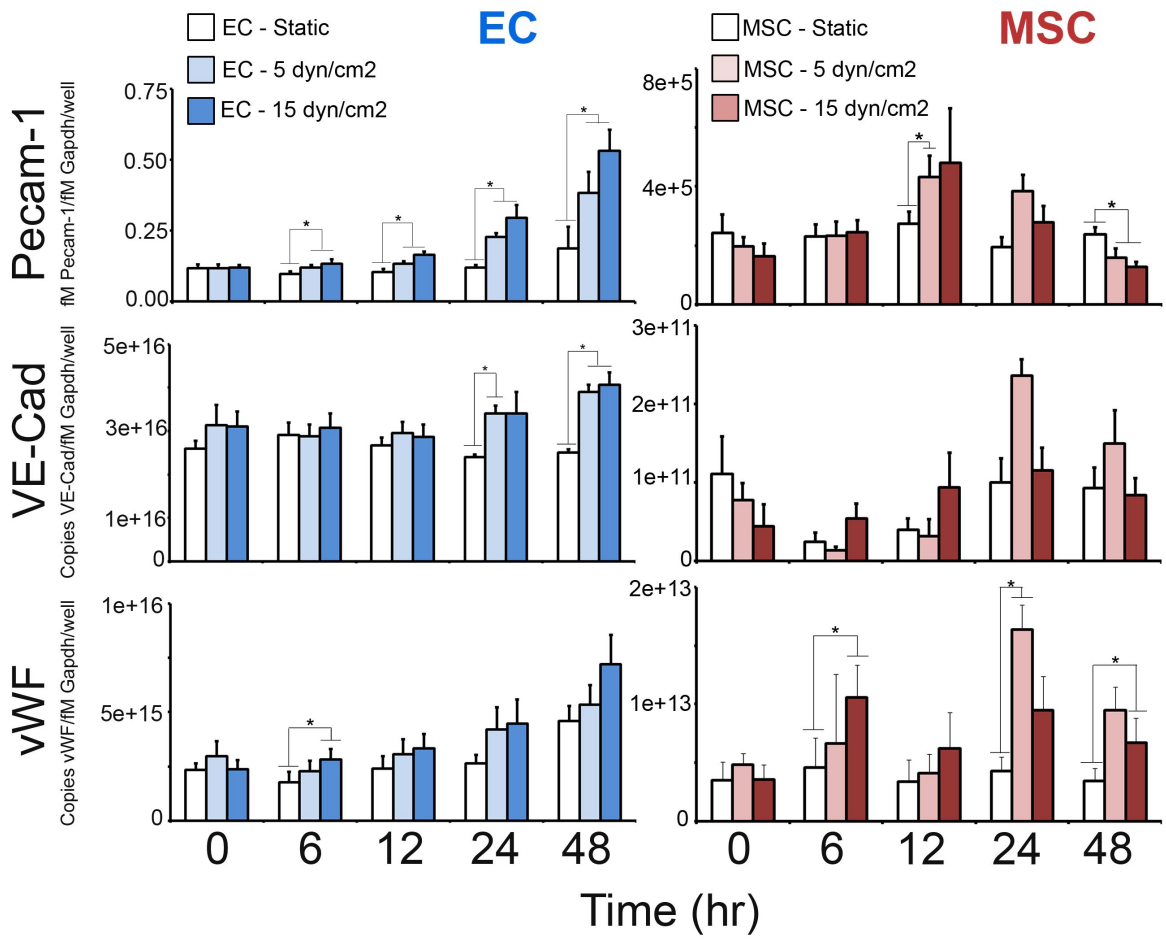


Figure 24: Kinetics of endothelial differentiation gene expression in response to applied shear stress. ECs (left, blue) and MSCs (right, red) were exposed to varied steady laminar shear stress magnitude (0, 5, or 15 dyn/cm^2) of varied duration (0, 6, 12, 24, or 48 hours). Asteriks indicate significant ($p \leq 0.05$,n=3-4) differences in gene expression relative to static controls.

at 6 hours was shear magnitude-dependent (p=0.011, n=3-4; $FC_{5dyn/sq-cm} 1.38 \pm 0.19$, $FC_{15dyn/sq-cm} = 1.72 \pm 0.21$) (Figure 26). MSCs expression followed a markedly different pattern. Pecam-1 and VE-Cad were expressed at very low levels in MSCs. Pecam-1 transiently and significantly increased following 12 hours applied shear stress (5 dyn/cm^2), but decreased significantly in both shear groups following 48 hours of applied shear. vWF was expressed in unstimulated MSCs (0 hr) and increased significantly after 6 (15 dyn/cm^2), 24 (5 dyn/cm^2), and 48 (15 dyn/cm^2) hours applied shear stress. Expression of endothelial differentiation genes was not shear magnitude-dependent in MSCs (Figure 26).

5.3.4 Shear response of immune and inflammatory genes

In addition to Pecam-1, VE-Cad, and vWF, ECs and MSCs were assessed for expression of five other common markers of physiologic ECs shear response, all related to immune and inflammatory function (Figure 25). Gene expression changes detected in ECs exposed to steady laminar shear stress were consistent with previous reports: Cox-2, eNos, Hmox1, and Klf2 increase. Mcp1 increased significantly only transiently (p=0.027, n=3-4; $FC_{15dyn/sq-cm} = 3.62 \pm 0.74$).

MSCs shear response pattern differed markedly from that of ECs for eNos, Klf2, and Mcp1. MSCs expression of eNos could not be distinguished from qPCR no template controls; application of shear stress did not significantly alter eNos expression. The transcription factor Klf2 was significantly altered in MSCs after 15 dyn/cm^2 shear stress, but at levels below the 1.5-fold detection limit for qPCR (p=0.024, $FC_{0hr} = -1.26 \pm 0.08$ and p=0.050, $FC_{24hr} = 1.22 \pm 0.09$). Mcp-1 expression was significantly decreased after 12 (15 dyn/cm^2), 24 (5 and 15 dyn/cm^2), or 48 (5 and 15 dyn/cm^2) hours applied shear stress, in contrast to the increase in Mcp1 observed in ECs after 12 hours applied shear. Significant Mcp-1 downregulation in MSCs remained relatively constant following applied shear stress of either 5 dyn/cm^2 ($FC_{avg} = 2.66 \pm 0.10$) or 15 dyn/cm^2 ($FC_{avg} = 3.73 \pm 0.73$)

Shear stress responses of ECs and MSCs were similar for Cox-2 and Hmox-1. MSCs expression of Cox-2 also increased in response to shear, but decayed more quickly than in ECs (12 hr vs. 48 hr). Cox-2 shear response in MSCs occurred within minutes at

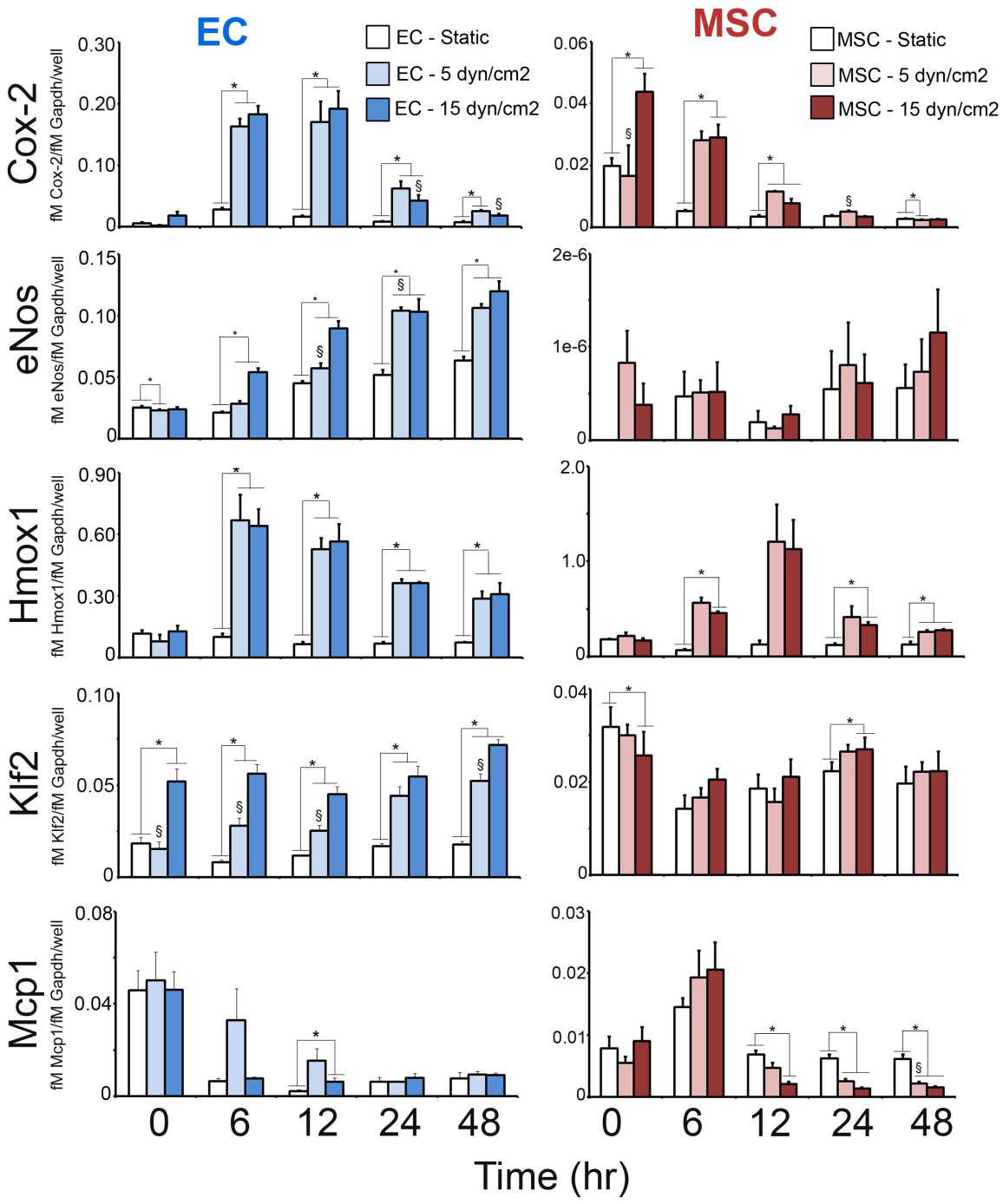


Figure 25: Kinetics of immune and inflammatory gene expression in response to applied shear stress. ECs (left, blue) and MSCs (right, red) were exposed to varied steady laminar shear stress magnitude (0, 5, or 15 dyn/cm^2) of varied duration (0, 6, 12, 24, or 48 hours). Asteriks indicate significant ($p \leq 0.05$,n=3-4) differences in gene expression relative to static controls. § indicates significant ($p \leq 0.05$,n=3-4) differences in gene expression levels between 5 and 15 dyn/cm^2 groups.

high shear magnitude (p=0.027, n=3-4; $FC_{15dyn/sq-cm} = 3.62 \pm 0.74$) and peaked after 6 hours (5̃-fold increase in both 5 and 15 dyn/cm^2 vs. static). Hmox1 shear-response was conserved between MSCs and ECs, increasing in both cell types. Expression of Hmox-1 peaked in both cells types after 12 hours applied shear, although this maximum represented a sharp peak in MSCs (12 hr) compared to a gradual decrease in Hmox-1 upregulation (6 - 48 hr) in ECs. Maximum Hmox-1 fold change was greater in ECs than MSCs ($FC_{ECs-max} = 10.1 \pm 3.6$ vs. $FC_{MSCs-max} = 8.1 \pm 3.6$).

5.3.5 Effect of shear magnitude on gene expression response

Cells were exposed to a low (5 dyn/cm^2) and high (15 dyn/cm^2) shear stress to approximate the differences in physiologic shear stress cues between small vessels and large vessels, respectively. More genes show shear-magnitude dependence in ECs than MSCs. Paired t-tests identified significant ($p \leq 0.05$, n=3-4) differences between shear magnitude groups for Cox2, eNos, Klf2, and vWF in ECs and for Cox-2 and Mcp1 in MSCs (Figure 24-25, §, and Figure 26, *). Figure 26 compares fold change differences over time and across cell type for genes whose expression varies significantly with shear magnitude (5 vs. 15 dyn/cm^2) in one or more conditions.

Higher magnitude shear stress in ECs resulted in a faster decrease in Cox2 upregulation after 24 and 48 hours applied shear. eNos expression in ECs was significantly different after 6 and 12 hours applied shear of either in 5 vs. 15 dyn/cm^2 groups, but the increase in gene expression at higher shear stress was moderate (6 hours: $FC_{5dyn/sq-cm} = 1.3 \pm 0.1$ vs. $FC_{15dyn/sq-cm} = 2.6 \pm 0.2$; 12 hours: $FC_{5dyn/sq-cm} = 1.3 \pm 0.04$ vs. $FC_{15dyn/sq-cm} = 2.0 \pm 0.1$). ECs expression of Klf2 was significantly different between low and high shear magnitudes after minutes (0 hour) and 6, 12, or 48 hours applied shear. In all cases, higher shear stress magnitude correlated with increased Klf2 expression. Like eNos shear magnitude differences, ECs expression of vWF significantly differed between groups after 6 hours applied shear stress, but the magnitude difference was slight ($FC_{5dyn/sq-cm} = 1.4 \pm 0.2$ vs. $FC_{15dyn/sq-cm} = 1.7 \pm 0.2$).

In MSCs, Cox2 was significantly upregulated within minutes (0 hour) only at high shear

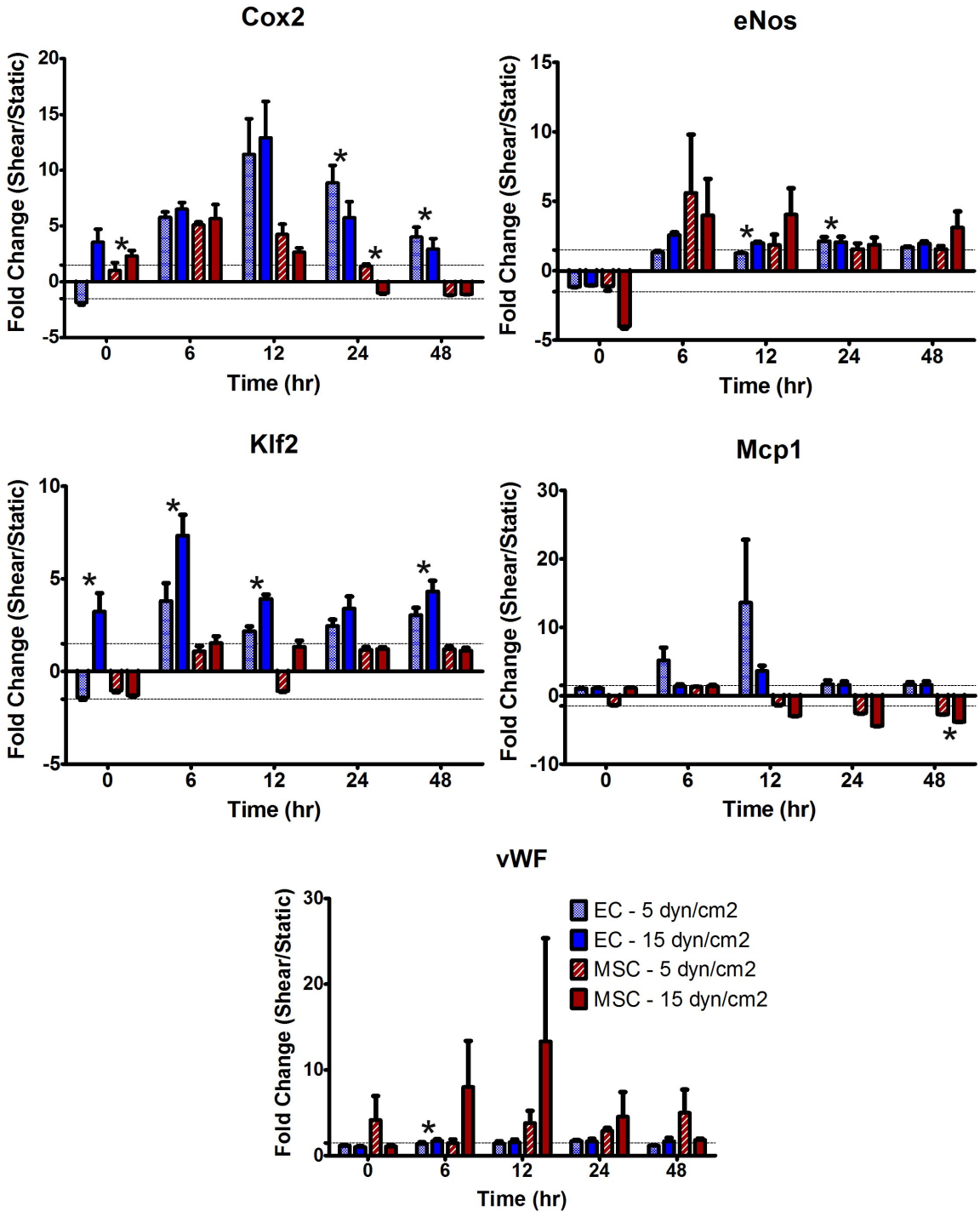


Figure 26: Shear-responsive gene expression is dependent on the magnitude of applied shear stress. Asterisks (*) indicate significant ($p < 0.05$, $n \geq 3$) differences in gene expression after 5 or 15 dyn/cm^2 magnitude applied shear stress, based on a paired t-test. Fold change values for 5 dyn/cm^2 (striped columns) and 15 dyn/cm^2 (solid bars) are shown for ECs (blue) and MSCs (red) for each timepoint. More instances of magnitude-dependent gene expression occur in ECs than MSCs.

magnitude (15 dyn/cm^2). Differences in shear magnitude effects were also significant at 24 hours, but did not pass the 1.5-fold change threshold. MSCs downregulation of Mcp1 was greater in 15 dyn/cm^2 samples after 12, 24, and 48 hours, although this difference was only significant after 48 hours ($FC_{5dyn/sq-cm} = -2.73 \pm 0.04$ vs. $FC_{15dyn/sq-cm} = -3.82 \pm 0.03$).

5.3.6 Correlation of protein expression with gene expression

Expression levels and spatial localization were assessed for PECAM-1, VE-CAD, and vWF protein to determine whether shear-responsive gene expression correlated with protein changes (Figure 27). For all three proteins, expression levels were lower in MSCs than ECs. In ECs, PECAM-1 increased significantly after 24 (FC=1.85; $p \leq 0.05$, $n \geq 3$) and 48 (FC=2.07; $p \leq 0.1$, $n \geq 3$) hours, similar to changes observed in gene expression. PECAM-1 expression in MSCs did not change significantly (p_{24h}=0.132, p_{48h}=0.348, $n \geq 3$) in response to shear stress. Confocal images show PECAM-1 is concentrated at cell-cell junctions in ECs, in contrast to diffuse staining in MSCs.

VE-CAD levels increased significantly ($p \leq 0.1$, $n \geq 3$) in ECs following 24 hours applied shear, but was no longer statistically significantly increased after 48 hours shear stress (p=0.511, $n \geq 3$). VE-CAD levels in MSCs also increased, albeit not significantly, after 24 hours (FC=1.64; p=0.375, $n \geq 3$) or 48 hours (FC=2.22; p=0.665), $n \geq 3$) applied shear stress. Spatial localization of VE-CAD was similar to PECAM-1 for both ECs and MSCs, showing cell-cell junction and diffuse staining, respectively.

vWF protein levels did not change significantly in either cell type after 24 or 48 hours applied shear stress. vWF protein was localized around nuclei in ECs, whereas vWF expression appeared diffuse throughout the cytoplasm in MSCs. Unlike PECAM-1 and VE-CAD, localization of vWF in ECs and MSCs was not uniform across a field of cells. In ECs, some cells showed intense perinuclear vWF staining [60], while other cells expressed comparatively undetectable levels of vWF. In MSCs, vWF protein localization was diffuse across all cells, but contained cell-scale elongated regions of intense staining.

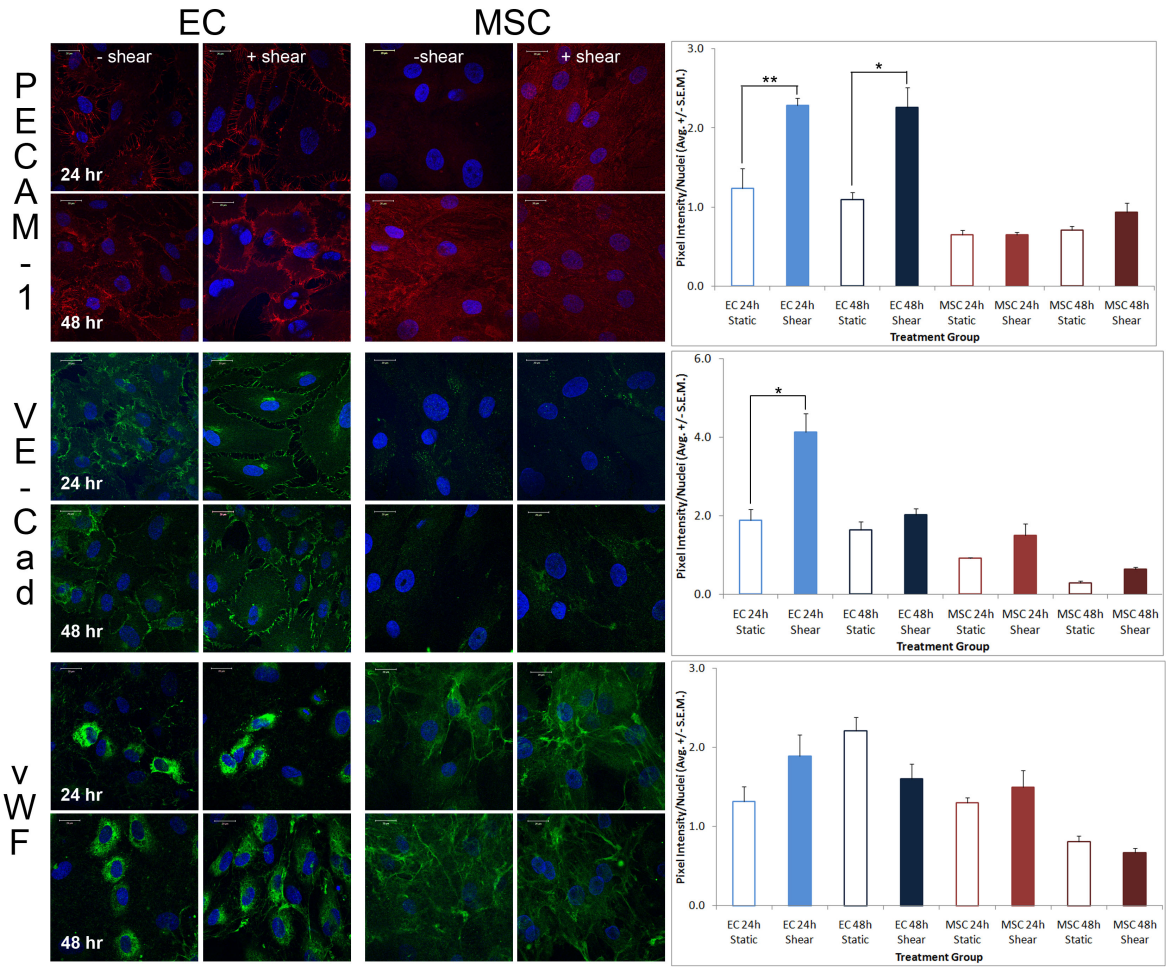


Figure 27: Protein expression in ECs and MSCs exposed to shear stress. Protein expression determined using immunocytochemistry for PECAM-1 (top two rows), VE-Cad (middle two rows), and vWF (bottom two rows). ECs (left two columns) and MSCs (middle two columns) images are shown, with intensity levels normalized to each image, in order to emphasize differences in protein localization between samples. To quantify changes in protein expression per cell, average pixel intensity per nuclei was quantified using unprocessed images (graphs).

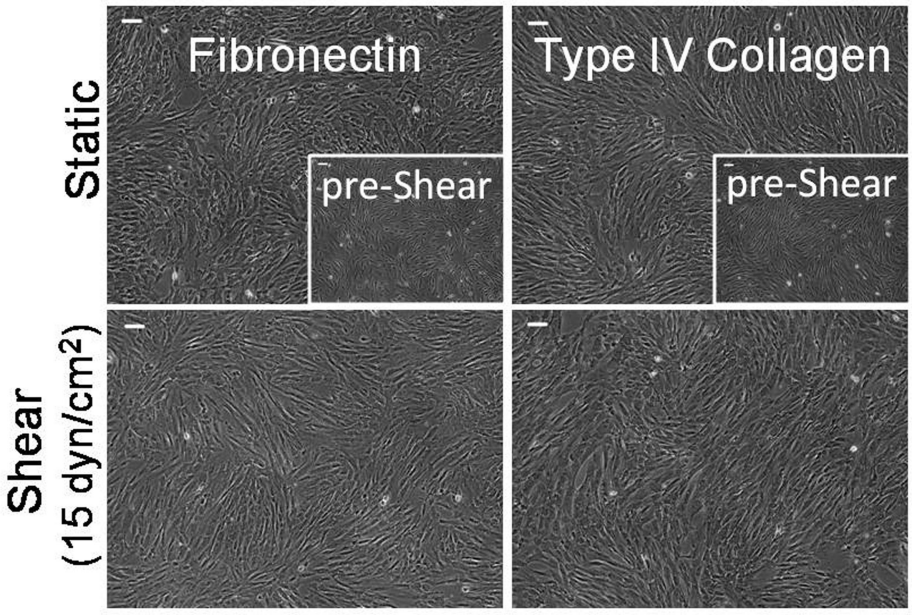


Figure 28: Effect of underlying protein substrate on MSCs response to applied shear stress. Comparison of shear on fibronectin-coated (left column) or type IV collagen (right column) morphology after 48 hours exposure to static (top row) or applied shear stress (15 dynes/cm^2; bottom row). Inset images show morphology immediately prior to application of shear stress. Altered protein substrate results in reduced rearrangement of MSCs in response to shear stress.

5.3.7 Shear-response varies with underlying protein substrate

Cell-matrix adhesions can affect how an applied force is mechanically translated to and chemically interpreted by cells [67, 104]. To determine whether the remodeling observed in MSCs exposed to shear stress on Type I Collagen-coated silicone was a function of cell-matrix interactions, MSCs were seeded on fibronectin- or Type IV collagen-coated silicone and exposed to 15 dyn/cm^2 shear stress for 24 hours. Cellular rearrangements were not as visible in shear samples of either Fibronectin or Type IV Collagen after 24 hours (Figure 28) as in MSCs exposed to shear stress on Type I Collagen (Figure 22).

5.4 Discussion

When exposed to shear stress on Type I Collagen-coated glass, MSCs do not form a confluent, aligned monolayer of cells as seen with ECs. Exposure of MSCs to shear stress

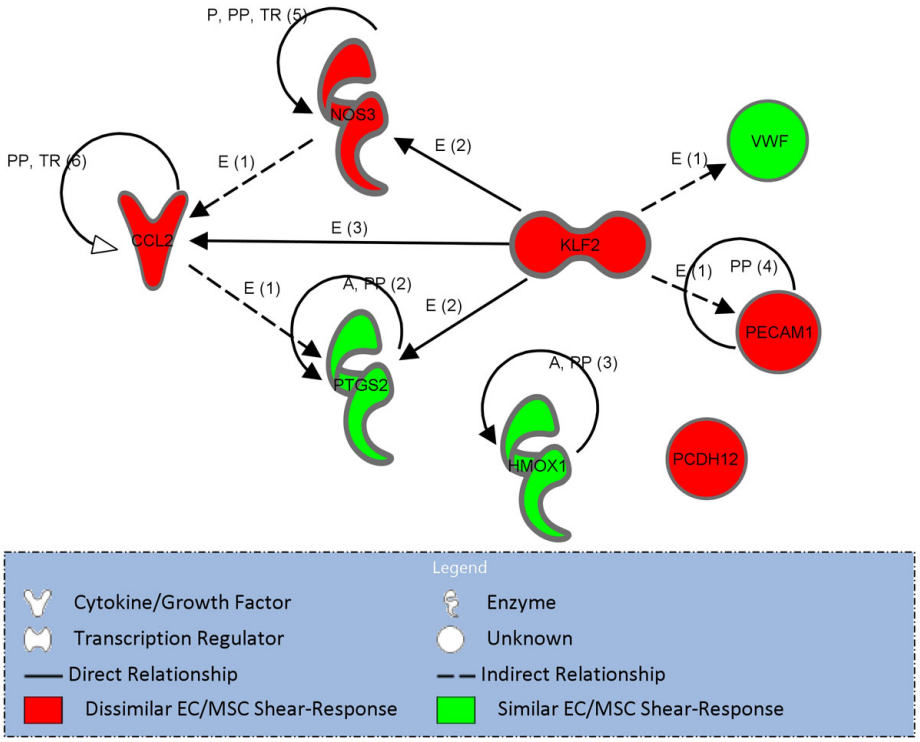


Figure 29: Schematic of known interactions between genes on immune and inflammatory marker panel. Connections between molecules are annoted with the relationship type and number of known relationships. Relationship types include: activation (A), expression (E), phosphorylation (P), protein-protein interactions (PP), or translocation (TR).

reduces cell number and results in appearance of a network of gaps and overlapping clusters and small areas of local alignment to the direction of shear stress. For the panel of 8 immune and inflammatory genes assessed, MSCs have lower expression levels compared to ECs (7 of 8 genes), reduced shear-responsiveness (49 vs. 22 instances), and slower response kinetics (3 vs. 6 genes significantly altered within 6 hours). MSCs alter signaling in response to applied shear stress, but do not correlate with endothelial differentiation. Application of shear stress significantly increases vWF expression in MSCs. This is not accompanied by upregulation of other endothelial differentiation-related genes, PECAM1 and VE-Cad, though, nor is vWF expression significantly shear-responsive in ECs. Different in protein quantities and spatial patterning indicate MSCs and ECs differ at both the gene and protein level.

A limited panel of gene and protein markers was used to infer the effect of shear stress on immune and inflammatory responses. A more complete assessment of immune and inflammatory response would include additional signaling molecules and functional assessments such as leukocyte adhesion. Low cell yield per sample ($\tilde{2}$50,000 cells/cm^2), due to bioreactor constraints and limited antibody availability, hindered protein quantification and spatial localization of all gene markers analyzed. Multiple time points (0-48 hours) and shear magnitudes (5 or 15 dyn/cm^2) provide data on a range of mechanical conditions. However, broader conclusions about shear threshold-sensing or signaling changes due to long-term mechanical conditioning could be made with a wider range of shear magnitudes and longer duration studies.

MSCs do not align in confluent layers parallel to the direction of applied shear, as ECs can within 48 hours. Further studies are needed to determine whether the lack of cell alignment parallel to the direction of applied shear stress is detrimental for a vascular therapy. Decreased cell number in MSCs samples exposed to shear stress may be caused by a decrease in proliferation or an increase in cell death [213, 15]. No significant decrease in cell viability suggests the decrease in cell number represents a physiologic, not pathologic, response. Furthermore, ECs are known to decrease proliferation in response to shear

stress [163], suggesting that mitosis regulation by mechanical shear stress may be a conserved morphological event. The cellular rearrangements observed in MSCs seeded on type I collagen in response to shear stress appear to be mediated by cell-matrix interactions, since shear-dependent MSCs rearrangements decrease when cells are seeded on type IV collagen- or fibronectin- coated surfaces. This response could be due to changes in signaling or mechanical stiffness inherent to the adsorbed protein molecule. Alternatively, differences in MSCs alignment and cellular rearrangement in response to shear stress could result from greater similarity of MSCs with other adherent cell types (e.g., fibroblasts), rather than ECs.

Other groups have reported that MSCs adopt endothelial traits in response to shear stress [205, 66, 304]. In these studies, gene expression levels of vWF, a late marker of endothelial differentiation, increased in MSCs in response to shear stress. However, neither protein levels of vWF nor increases in expression of earlier markers of ECs differentiation, Pecam-1 and VE-Cad, were observed. This data suggest 48 hours of applied shear stress at either 5 or 15 dyn/cm^2 is not sufficient to trigger endothelial-like differentiation in MSCs. Differences from O'Cearbhaill *et al* and Dong *et al* results may be due to marked differences in applied mechanical cues, 2-D vs. 3-D culture environments, or MSCs species [66, 205]. Bai *et al* tested the effect of shear magnitude with or without VEGF stimulation on expression of the VEGF receptor, Flk1, another marker of ECs [8]. Flk1 increased transiently in MSCs in response to shear stress (10-20 dyn/cm^2), decreasing by 48 hours. This is consistent with a response in MSCs of endothelial-relevant markers to shear stress, without clear differentiation along an endothelial lineage. Protein quantification of Pecam1, VE-Cad, and vWF was consistent with ECs gene changes. No significant differences in MSCs expression of Pecam1 or vWF protein though indicates slower kinetics or post-transcriptional regulatory mechanisms at work.

Exposure of ECs to applied shear stress promoted an anti-inflammatory environment with increased expression of cell-cell adhesion molecules, Pecam1 and VECad. Expression of clotting-related molecule vWF increased, albeit not significantly, in ECs. The significant decrease in Mcp1 and Pecam1 observed in MSCs suggests these cells may have

reduced monocyte and leukocyte adhesion compared to ECs. Significantly increased expression of vWF in response to shear stress may promote clotting [159], a factor that may impact success of an MSCs-based therapy in which cells experience shear stress. MSCs exposed to shear stress matched the upregulation of Cox-2 and Hmox-1 observed in ECs. eNos expression was undetectable in MSCs, but studies by others have shown transduced MSCs can signal through eNos [126]. Klf2 expression was highly upregulated in ECs in response to shear ($\tilde{5}$-fold increase after 6, 12, 24, and 48 hours in both 5 and 15 dyn/cm^2). The lack of Klf2 expression in MSCs suggests MSCs will not upregulate the downstream targets of Klf2, highlighting another difference in MSCs and ECs signaling.

MSCs and ECs differed in protein levels and localization of endothelial-relevant markers, Pecam1, VE-Cad, and vWF. For all three markers, MSCs expressed lower levels and showed more diffuse staining than ECs. Differences in significantly shear-responsive gene expression versus protein expression levels (PECAM1: MSCs-48hr; VE-Cad: ECs-48hr; vWF: MSCs-24hr and MSCs-48hr) demonstrate that gene and protein levels are independently regulated. The impact of shear-responsive changes at the gene expression level may be modified by subsequent post-transcriptional changes. Differences in protein localization highlight the importance of post-translational mechanisms also in regulating cell signaling responses to applied shear stress. For example, non-uniform distribution of vWF protein suggests vWF localization is actively regulated in ECs (presence/absence; perinuclear vs. cytoplasmic distribution) [114] and MSCs (regions of concentrated expression, possibly adjacent to cell membranes). Specialized functions of ECs may rely on protein modification mechanisms to achieve physiologic signaling.

ECs signaling was more sensitive to shear stress magnitude than MSCs, suggesting more refined mechanosensing capacity in ECs. This may be due to extended preconditioning of the cells during development and adult function, similar to methods reported to benefit *in vitro* cultures [189]. For the two shear magnitudes tested (5-15 dyn/cm^2), MSCs appear to respond in a binary manner. Only Cox2 immediate signaling (0 hr timepoint) and Mcp1 signaling at 48 hours showed significant differences in expression between 5 and 15 dyn/cm^2. Testing a larger range of shear magnitudes would determine whether additional

critical signaling thresholds exist (e.g., minimum or maximum induced signaling).

5.5 Conclusions

In summary, this data show MSCs and ECs differ in terms of basal gene and protein expression levels, protein localization, response to applied shear, and kinetics of shear-response. Differences in shear-responsive signaling are summarized in Figure 29, with similar responses between MSCs and ECs for Cox2, Hmox1, and vWF and dissimilar responses for eNos, Klf2, Mcp1, Pecam1, and VE-Cad. These signaling differences suggest MSCs may promote a low-inflammatory, low immunogenic environment when exposed to shear stress as part of a cell therapy. MSCs remodeling in response to shear stress and failure to upregulate characteristic endothelial markers suggest additional cues may be required if MSCs are to be used as endothelial layer substitutes. This study also demonstrates the dependence of MSCs mechanoresponse on the cell-matrix attachment mechanism, with different responses observed for type I collagen compared to type IV collagen or fibronectin.

5.6 Materials and Methods

Supplies Cells and bullet kit media for early passage cells were purchased from Lonza. Lab-made culture media components included MSCs-qualified serum (Atlanta Biologicals); penicillin/streptomycin, EGF, and IGF-1 (Gibco); hydrocortizone, VEGF, and ascorbic acid (Sigma); recombinant human bFGF (PeproTech), fetal bovine serum (MediaTech). Shear stress was applied on glass slides coated with either rat tail Type I Collagen (BD Biosciences), mouse Type IV Collagen (BD Biosciences), or human plasma Fibronectin (Gibco). Parallel plate shear loops were fabricated as previously described [155]. Gene expression was assessed using reagents for RNA isolation (Qiagen), cDNA synthesis (Invitrogen), standard qPCR (ABI), and custom-synthesized primers (Invitrogen). Immunostain reagents were purchase for donkey serum (Sigma); primary antibodies PECAM-1 (Millipore), VE-CAD (Santa Cruz Biotechnology), and vWF (Dako); and secondary antibodies

Cy3-conjugated donkey anti-mouse IgG (Jackson Immunoresearch), and AlexaFluor 488-conjugated donkey anti-goat and anti-rabbit IgG (Invitrogen).

Cell culture of MSCs & ECs Human adult bone marrow-derived mesenchymal stem cells (MSCs) and aortic endothelial cells (ECs) were cultured according to manufacturer's recommendations (Lonza). MSCs were expanded in MSCs bullet kit media and frozen at Passage 5. MSCs were thawed at P.5 and used in shear stress experiments at P.6 using lab-made media: high-glucose DMEM with 10% MSCs-qualified serum , 2mM L-glutamine, 1% penicillin/streptomycin. MSCs at experimental use passage were characterized for expression of protein surface markers and differentiation potential along osteogenic, chondrogenic, and adipogenic lineages. ECs were expanded to P.3 in bullet kit media and frozen. ECs were thawed in lab-made media (MCDB-131 with 5% FBS, 1% penicillin/streptomycin, 1% L-glutamine, 0.001 mg/ml hydrocortizone, 0.002 μg/ml FGF, 0.010 μg/ml EGF, 0.002 μg/ml IGF, 0.001 μg/ml VEGF, and 50 μg/ml ascorbic acid). To conserve growth factor use, ECs were subjected to shear stress in MCDB-131 with 5% FBS, 1% penicillin/streptomycin, 1% L-glutamine, 0.0005 μg/ml EGF, and 0.002 μg/ml FGF.

Applied shear stress Steady laminar fluid shear stress was applied using a parallel plate shear system, as previously described [155]. Briefly, media circulated continuously through a reservoir, peristaltic pump (McMaster-Carr), pulse dampener, and slide chamber with defined flow containing a cell-seeded, protein-coated glass slide. Prior to and following applied shear, cells were visualized with phase images using an Axiovert microscope (Zeiss) and SPOT software (Diagnostic Images).

Cell Number and Viability MSCs were exposed to 15 dyn/cm^2 shear stress or parallel static culture for 48 hours. Cell number and viability was quantified for trypsinized cells using a Vi-CELL Series Cell Viability Analyzer (Beckman Coulter).

Gene Expression RNA was isolated, cDNA synthesized from 0.5 μg RNA, and gene expression levels quantified using qPCR as previously described [67]. Primers were designed using Primer Express 3 software (ABI). Four replicates were generated per cell type (ECs or MSCs) per time point (0, 6, 12, 24, or 48 hr) and per force condition (0 - Static, 5 dyn/cm^2, or 15 dyn/cm^2), for a total of 120 samples. A randomized design was used to

minimize effects due to experimental variation. Target gene levels (fM) were normalized to the housekeeping gene Gapdh (fM). Although Gapdh expression in ECs decreased significantly ($p < 0.05$, n=3-4) in response to 48 hours shear stress at either 5 or 15 dynes/cm^2, this was below the detection limit cut-off of 1.5-fold. Due to technical errors (shear sample leakage or RNA too dilute for cDNA synthesis), statistical analysis of gene expression could not be completed for MSCs subjected to 5 dyn/cm^2 for either 6 or 24 hours (shear groups: n=2). Connections between signaling molecules were determined with Ingenuity Pathways Analysis software (IPA).

Protein distribution and quantification Protein expression was assessed using antibody staining and confocal imaging. MSCs and ECs were seeded on Type I Collagen-coated glass slides and exposed to 15 dyn/cm^2 shear stress or parallel static culture for 24 or 48 hours. Samples were fixed in 4% formaldehyde and stored in PBS at 4°C prior to staining. Samples were permeabilized with 0.05% Triton-X for intracellular markers (VE-Cad and vWF), blocked in 5% donkey serum/0.1% BSA in PBS, stained overnight at 4°C in primary antibody (1/100 dilution) and secondary antibody (1/100) for 1 hour at room temperature, and counterstained with Hoechst 33258 to label nuclei. Samples were imaged on a Zeiss LSM 510 META confocal microscope. A ratio of average image pixel intensity per number of nuclei was calculated for each image using measurements made in Image J (NIH). Unpaired t-tests for each cell type were completed to determine significant differences between applied shear and static culture conditions. Following quantification of protein levels on raw image files, all images were processed for auto-contrast in Photoshop (Adobe) and compared across groups to highlight patterning differences between cell type and force conditions. To enable comparison between treatment groups, ECs and MSCs samples were antibody stained together and imaged using the same confocal laser settings.

Protein substrate studies To determine the effect of underlying protein substrate on resulting shear response, glass slides were coated using 5μg/cm^2 solutions of Type I Collagen, Type IV Collagen, or Fibronectin.

Statistical analysis Unless otherwise stated, significance is defined as $p \leq 0.05$. Multifactorial ANOVA was used to determine differences in gene expression due to cell type, force condition, or treatment duration. Paired and unpaired t-tests were used to compare static and shear gene expression samples and protein data, respectively, appropriate to the experimental design.

CHAPTER VI

TRANSCRIPTOME COMPARISON OF MESENCHYMAL STEM AND AORTIC ENDOTHELIAL CELL RESPONSE TO VASCULAR-RELEVANT APPLIED FLUID SHEAR STRESS

6.1 Abstract

Development of cell-based therapies to treat endothelial dysfunction will decrease the high personal and financial cost of vascular disease. To evaluate the potential of mesenchymal stem cells as endothelial cell substitutes, transcriptome responses to vascular-relevant levels of fluid shear stress were compared between human adult bone marrow-derived mesenchymal stem cells (MSCs) and human aortic endothelial cells (ECs). Cells seeded on fibronectin-coated glass slides were exposed to steady laminar shear stress (15 dyn/cm^2) for 24 hours. RNA was isolated and pooled (n=4 samples/group) from shear and parallel static cultures for each experiment; pooled RNA (n=3 experiments per cell type) was assessed using whole human genome microarrays. Results were validated with literature comparisons and qPCR. Microarray samples group according to cell type and force condition, via principal component analysis. Shear-responsive transcriptomes, defined as the set of genes with significantly (paired t-test $p < 0.05$) altered expression of at least 1.5-fold, identified 5590 and 1772 genes for ECs and MSCs, respectively. Conserved shear-responsive genes met paired t-test and fold change criteria in both cell types, as well as significant ($p < 0.05$) force-dependent gene expression as determined using two-factor ANOVA. Analysis of the set of 574 probes meeting this 'conserved' shear-response definition identified shared traits of shear-responsive genes, including: correlation of shear-responsive genes with chromosomes 4, 11, and 17; uneven cellular location and molecular function distribution; potential regulatory signaling nodes including transcription factors and highly linked molecules; and evidence that cell cycle functions are regulated by shear stress, independent of cell type. This data demonstrate MSCs mimic relatively few of the

gene expression responses to shear stress present in ECs. Combined with morphological differences in cell response to shear stress, this data suggests MSCs cannot be assumed to mimic ECs mechanosignaling responses.

6.2 Background

Endothelial cells (ECs) respond with unique signaling changes to different types of shear stress, including oscillatory versus steady, laminar versus turbulent, and varied duration applied shear stress [78, 208, 61]. These signaling changes have been studied through numerous studies using both high-throughput and single factor approaches. Shear-responsive signaling changes in ECs help regulate a broad range of functions including proliferation, migration, inflammatory and immune activation, and angiogenesis [58, 309, 78]. The ability to signal appropriately in response to shear stress has been used as a metric to evaluate cell-based therapies designed to repair, replace, or regenerate vascular endothelium [185, 326]. Whole genome microarray characterization of the ECs and mesenchymal stem cell (MSCs) responses to shear stress enables rapid identification of RNA-based similarities and differences in mechanosignaling.

Shear stress is involved in prevention and progression of vascular diseases, notably atherosclerosis [58, 57]. Microarray data has contributed in multiple ways to knowledge of ECs shear-response. Endothelial cells derived from different regions of the vasculature respond to shear stress differently [36, 181, 27, 208]. Dai *et al* used finite element analysis to determine shear flow profiles in human carotid arteries in areas of high and low probability atherogenesis [53]. Subsequent microarray analysis of HUVECs exposed to these profiles identified genes sensitive to either atheroprone or atheroprotective shear regimens. High-throughput signaling analysis of endothelial cells exposed to steady laminar shear stress at physiologic levels (10-25 dyn/^{2}) identify anti-apoptotic, anti-proliferative, anti-oxidant, and pro-differentiative effects [309]. Microarray analysis has also been used to track differences in endothelial shear-response due to co-culture [98].

While numerous high-throughput studies describe the response of ECs to shear stress, few have investigated how potential ECs cell substitutes respond to shear stress. Stem

cells proposed as ECs substitutes include embryonic stem cells (ESCs), mesenchymal stem cells and MSCs-like cells such as adipose-derived stem cells (ADSCs) and amniotic fluid-derived cells (AFSCs), and endothelial progenitor cells (EPCs). Embryonic stem cells respond to vascular-relevant levels of shear stress with upregulation of early endothelial-differentiation markers (Ahsan and Nerem, unpublished). Embryonic stem cells differentiated towards ECs respond to applied shear stress similarly to ECs [185]. AFSCs pre-differentiated towards ECs also respond similarly to endothelial cells [326]. ADSCs exposed to shear stress upregulate endothelial-relevant markers nitric oxide and VEGF, but not markers characteristic of ECs differentiation [15]. EPCs are closest to ECs in terms of differentiation lineages. In response to shear stress, EPCs differentiate towards and respond similarly to ECs [321, 323, 278, 279]. These studies of stem cell shear-responsiveness typically focus on a few assessments, rather than broader response profiling using high-throughput techniques.

MSCs are a promising therapeutic stem cell source to their relative ease of access, potential for autologous therapy, immunomodulatory and paracrine signaling effects, and fewer ethical concerns related to cell origin. Studies of MSCs response to shear stress have focused on immediate cell signaling [142], orthopedic cell responses [81], and vascular responses [15, 66]. Microarray analyses have been used to monitor MSCs mechanoresponses to cyclic strain [146, 218] and for preliminary analysis of shear stress-responsive signaling at low magnitudes (1 dyn/cm^2) [81]. More than 150 studies have employed microarrays to study MSCs signaling changes as a function of: tissue source ; donor age/cell passage differentiation along classic lineages - osteogenic, chondrogenic, and adipogenic and in vitro culture environments .

Parallel cell type comparisons have been used to study mechanosensing in different types of vascular cells (endothelial vs. smooth muscle [228]; vascular vs. valvular ECs [27]; EPC vs. ECs [24]), fibroblasts (tendon, cornea, skin [171]), and bone cells (osteoblasts vs. osteoclasts [125]). One studied compared the response to applied force between more distantly related cell types (ECs vs chondrocyte response to shear stress [96]). We combined

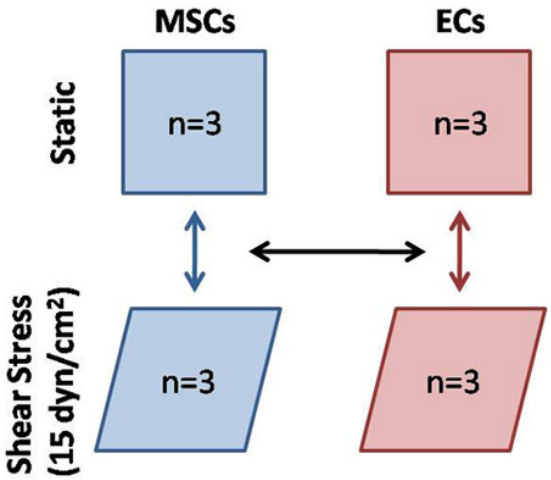


Figure 30: Schematic of shear stress microarray experimental design. MSCs and ECs transcriptomes were compared using whole genome microarray comparison. Paired t-tests for three independent experiments were completed for each cell type (vertical arrows), followed by comparison of shear responses across cell type (horizontal arrow).

these two approaches, highthroughput expression detection via microarrays and comparative cell type analysis, to study the response to vascular-relevant levels of steady laminar shear stress of human aortic endothelial cells and human adult bone marrow-derived mesenchymal stem cells. This signaling analysis highlights vascular-relevant functions that MSCs may be suited or ill-matched to mimic.

6.3 Results

6.3.1 Morphology of ECs and MSCs in response to applied shear stress

ECs and MSCs were exposed to 15 dyn/cm^2 steady laminar shear stress on fibronectin-coated glass slides for 24 hours in their respective culture media. Three independent experiments per cell type were completed, with four independent samples per group per experiment (Figure 30). Representative phase images of MSCs and ECs are shown in Figure 31. Within 24 hours, local regions of ECs monolayers align parallel to the direction of applied shear stress (Figure 31B vs. A). ECs appear less dense in samples exposed to shear stress than those exposed to static culture, consistent with other reports that shear stress decreases ECs proliferation. In contrast, MSCs were larger in adherent size than ECs; spindle-shaped after both static or applied shear stress, in contrast to ECs

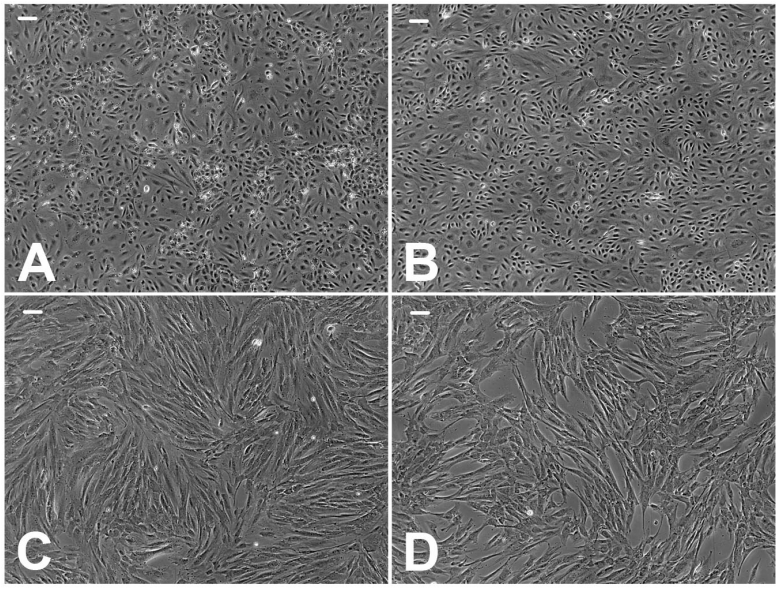


Figure 31: Comparison of cell morphology in response to shear stress. Phase images of ECs (A, B) and MSCs (C, D) after either static (A, C) or 15 dyn/cm^2 steady laminar shear stress (B, D) culture for 24 hours on fibronectin-coated silicone. Shear stress was applied in the horizontal direction, relative to these images.

cobblestone morphology; and did not align to the direction of applied shear stress. Small gaps between cells were visible in MSCs samples exposed to shear stress, compared to parallel static, confluent cultures.

6.3.2 Overview of microarray results

Principal component analysis and two-factor ANOVA provide global overviews of microarray data, differentiating sample and gene expression patterns. The twelve pooled microarray samples can be clearly separated by cell type (MSCs: blue; ECs: red) along principal component 1, and by force condition (arrows) along principal component 2 (Figure 32C) or 3 (Figure 32A). Both 3-D and 2-D representations of PCA are shown for easier visualization of paired sample distribution and force condition and cell type separation, respectively. The marked differences in gene expression profiles between cell type are corroborated by two-factor ANOVA, in which 18,735 genes (5̃0% of the total assessed) have expression significantly dependent on cell type versus 7078 (1̃6%) or 3161 (7̃%) genes vary significantly with force condition or an interaction effect, respectively (Figure 32B) .

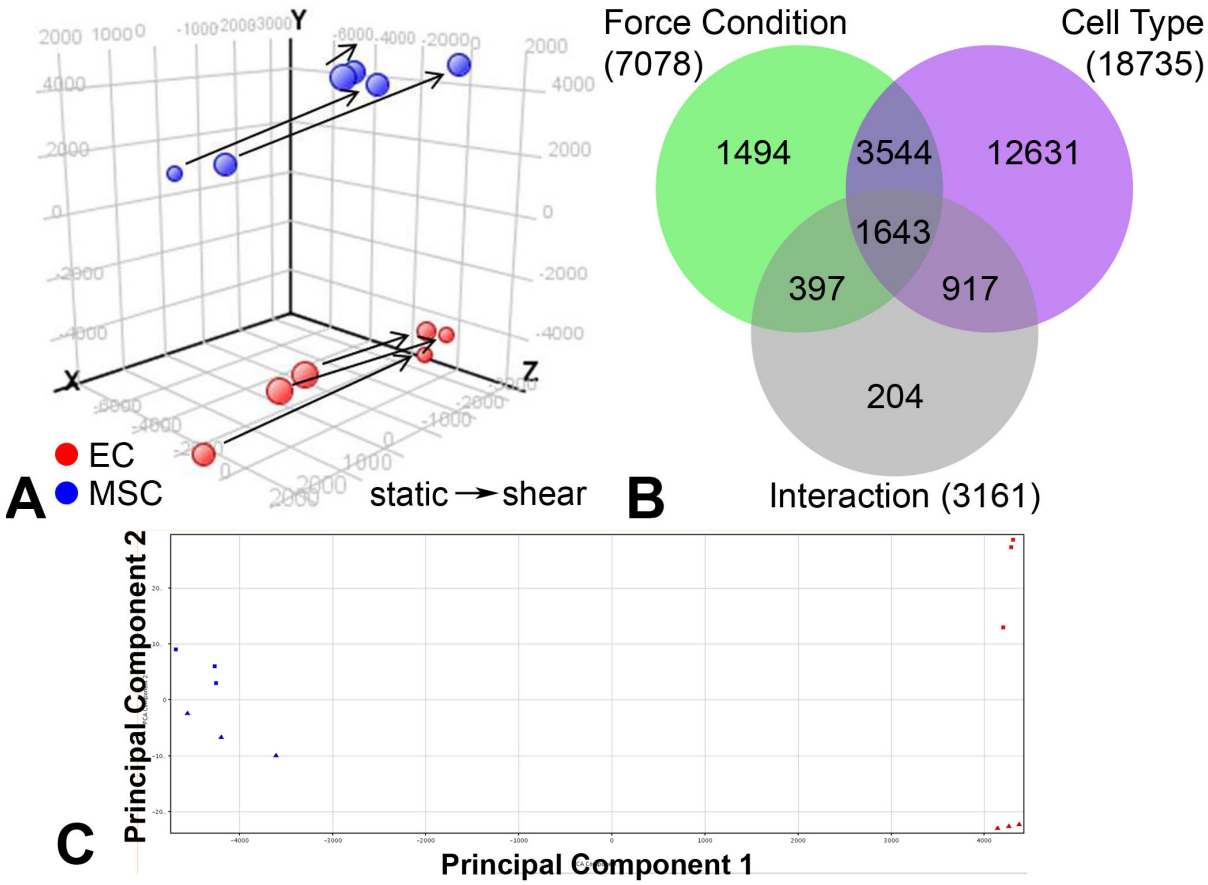


Figure 32: Overview of microarray analysis of ECs and MSCs samples exposed to applied shear stress (15 dyn/cm^2). Cells were seeded on fibronectin-coated glass and exposed to shear stress using a parallel plate shear system for 24 hours. (A) 3-D principal component analysis separates ECs and MSCs samples according to principal component 1 (y-axis). Shear and static samples separate along principal component 3 (x-axis). (B) Venn diagram showing two-factor ANOVA results. Within the set of genes present or marginal in at least one of 12 arrays, expression of 18735, 7078, and 3161 probes was significantly (corrected p-value < 0.05, n=3) dependent on cell type, force condition, or an interaction of the two parameters. (C) 2-D principal component analysis showing separation of cell type (principal component 1, horizontal) and force condition (principal component 2, vertical) for MSCs (blue) and ECs (red) samples exposed to static (squares) or shear (triangles) conditions.

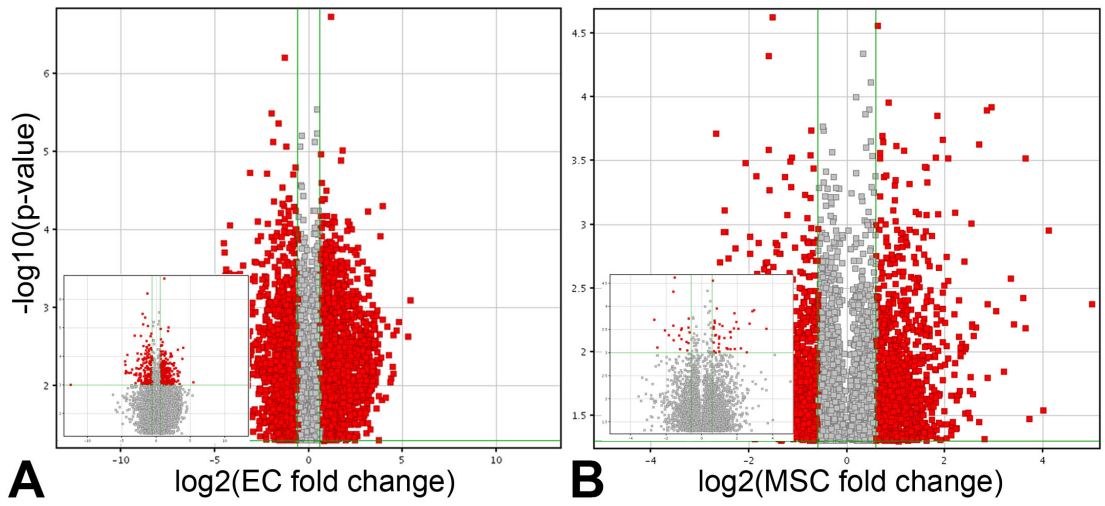


Figure 33: Volcano plots comparing significance and fold-change distributions of gene expression changes due to applied shear stress. Red squares indicate genes whose expression alters significantly ($p < 0.05$ or, inset, $p < 0.001$) by $\geq$1.5-fold in ECs (A) or MSCs (B). In ECs, 462 and 5590 genes meet fold-change and either high or low significance criteria, respectively. Fewer genes were identified in MSCs: 55 or 1775 genes met fold-change and either high or low significance criteria.

Volcano plots, shown in Figure 33, show the distribution of significantly shear-responsive genes in ECs (Figure 33A) or MSCs (Figure 33B). Approximately 10 times as many genes are shear-responsive in ECs as MSCs at high significance cut-offs ($p < 0.001$ & $|FC| > 1.5$: 462 vs. 55). At lower significance cut-offs ($p < 0.05$ & $|FC| > 1.5$), approximately 5 times as many genes were shear-responsive in ECs compared to MSCs (5590 vs. 1775). The MSCs distribution on the volcano plot is narrower and includes more genes at low p-values than the ECs distribution. Average gene variation in MSCs ranges from $\pm$4-fold, in contrast to $\pm$16-fold in ECs. Shear-responsive genes change less significantly in MSCs than ECs by two orders of magnitude (minimum p-values: $10^{-4.5}$ $vs.$ $10^{-6.5}$). MSCs do respond to shear stress above fold-change and significance thresholds, but in lower numbers, magnitude change, and peak significance compared to ECs.

6.3.3 Shear-responsive genes identified in MSCs and ECs

Two-tailed paired t-tests were used to identify shear-responsive genes in each cell type. In ECs, paired t-test analysis with Benjamini-Hochberg MTC identified 361 genes significantly (corrected p-value< 0.05) altered by shear stress, 267 of which alter by at least

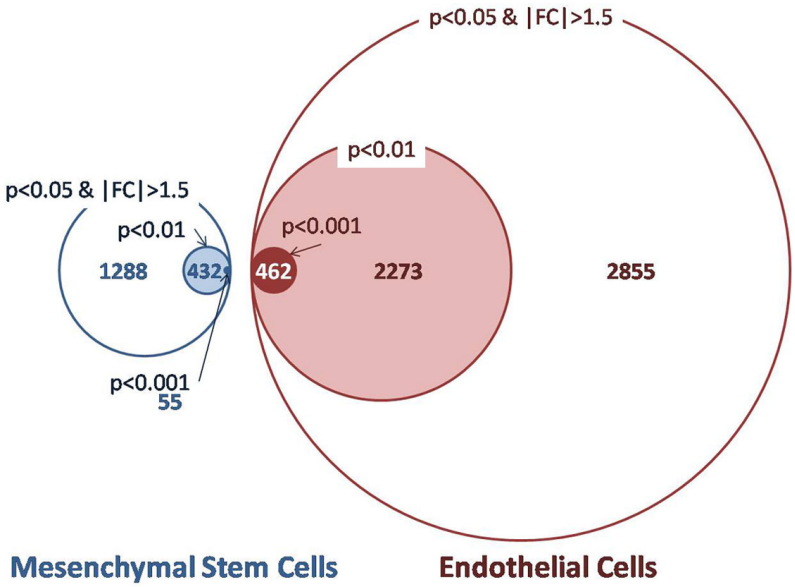


Figure 34: Nested loops of MSCs and ECs shear-responsive genes identified via paired t-test. Genes with expression levels differing by at least 1.5-fold between applied shear and static samples are shown for three levels of increasing significance: $p < 0.05$, outermost line; $p < 0.01$, middle shaded region; and $p < 0.001$, innermost dark shading. MSCs (left, blue) and ECs (right, red) data represents three microarrays of pooled RNA per shear and static group. Multiple testing corrections not applied because no genes were identified in MSCs using this method. Circle size is proportional to gene number.

1.5-fold regulation. Application of multiple testing corrections (Benjamini-Hochberg MTC; Bonferroni FWER; FDR) resulted in a null set for MSCs significant shear-responsive genes. Thus, in order to have consistent data analysis of all samples and allow subsequent cell type comparisons, multiple testing corrections were not applied to either cell type. More stringent significance levels in combination with fold change thresholds were applied to decrease the number of false positives identified due to technical or statistical error or biological noise. Genes in MSCs and ECs with significance ($p < 0.05$) and magnitude fold change ≥ 1.5 number 1775 and 5590, respectively. Increasing the significance threshold narrows the list of shear-responsive genes at median stringency ($p < 0.01$: 487 genes in MSCs vs. 2735 genes in ECs) and high stringency ($p < 0.001$: 55 genes in MSCs vs. 462 in ECs). The relative abundance of shear-responsive genes in ECs vs. MSCs and in response to varied selection criteria are illustrated by a nested Venn diagram (Figure 34).

6.3.4 Global gene expression responses of MSCs and ECs to shear stress

Venn diagram overlays of the results of two factor ANOVA and paired t-tests in ECs and MSCs were used to triangulate on a list of 'conserved' shear-responsive genes (i.e., the intersection region of these three circles in the Venn diagram). At lowest t-test significance values ($p < 0.05$), 574 probe names are identified in the conserved shear-responsive set (Figure 35A). At the most stringent significance cut-offs ($p < 0.001$), no genes are identified with conserved shear-response (Figure 35B). Furthermore, fewer shear-responsive genes from the original list ($p < 0.05$) in MSCs meet this high stringency criteria (55/1775; 3%) compared to ECs (462/5590; 8%). At the intermediate significance level ($p \leq 0.01$), 2735 and 487 genes were significantly altered in ECs and MSCs, respectively. 100 genes of this set were significant in both ECs and MSCs paired t-tests ($p < 0.01$; $|FC| \geq 1.5$) and two-factor ANOVA force-dependence (corrected p-value < 0.05). 15 genes were identified as significant by both paired t-tests, but not two-factor ANOVA. These probe names may be either false positives from the t-tests or genes whose shear-sensitivity is based on initial conditions. In the latter case, only paired static/shear analysis would detect a significant shear-response, while unpaired statistical tests such as the two-factor ANOVA might miss

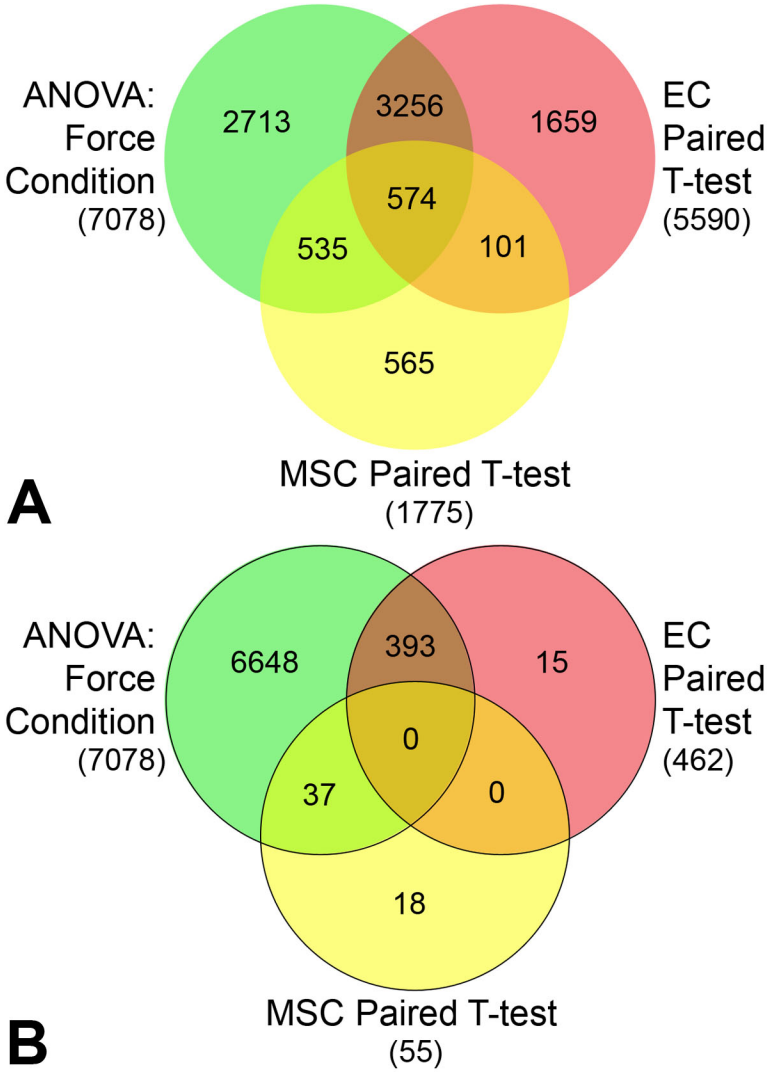


Figure 35: Venn diagram representation of shear-responsive genes in MSCs and ECs. Genes were identified using two-factor ANOVA force-dependence corrected p-value< 0.05 (green circle), paired fold change of at least 1.5-fold and significance cut-off in ECs (red circle), and paired fold change$\geq$1.5 and significance cut-off in MSCs (yellow circle). Two significance levels for paired t-tests are shown: (A) paired t-test $p < 0.05$ and (B) paired t-test $p < 0.01$. Multiple testing corrections were not applied since no genes were identified in MSCs using this method.

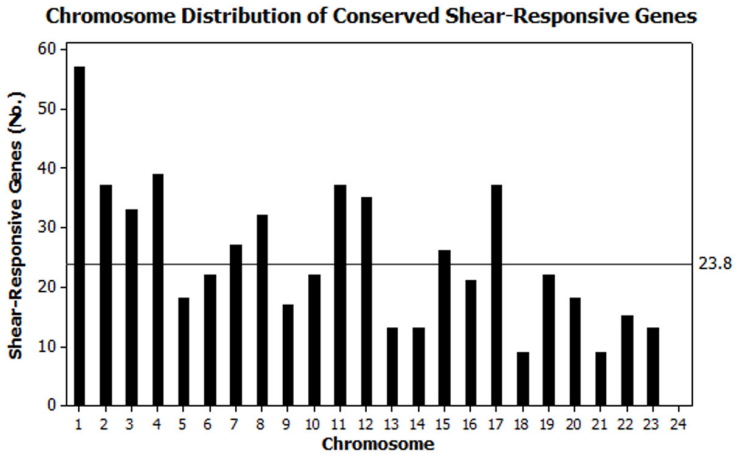


Figure 36: Distribution of conserved shear-responsive genes across chromosomes. The set of 574 conserved shear-responsive probes are distributed across chromosomes ($\mu = 23.8, \sigma = 12.7$). Chromosomes 23 and 24 refer to the X and Y sex chromosomes, respectively. As expected given the use of female cell sources in this analysis, no shear-responsive genes were identified on the Y-chromosome (24).

this relationship. For subsequent signaling analysis, the set of conserved shear-responsive genes was defined using a significance level of $p < 0.05$. A list of these genes is included in Appendix D, Table 15.

6.3.5 Distribution of conserved shear-responsive genes across chromosomes

Shear-responsive genes are distributed across the set of 23 chromosomes, with an average of 23.8±12.7 genes per chromosome (Figure 36). No conserved shear-responsive genes were present on the Y-chromosome in this analysis, consistent with the use of female donors for ECs and MSCs. To determine whether shear-responsive genes correlate with chromosomal properties, a normal distribution was assumed for shear-responsive genes per chromosome, per total gene, and per length of DNA. Significance correlation of shear-responsive genes with these chromosomal properties was determined based on 68, 95, or 97% confidence intervals. Chromosome 1 (57 genes) contained more shear-responsive genes per chromosome (95% C.I.); chromosomes 2 (37), 4 (39), 11 (37), 17 (37), 18 (9), and 21 (9) also varied from the average number of shear-responsive genes per chromosome by more than one standard deviation (68%). The distribution of shear-responsive genes per number of genes was 0.023±0.023 ($\tilde{1}$ shear-responsive gene/43

total genes). Chromosomes 11 (0.098; 97% C.I.) and 4 (0.087; 95% C.I.) contained significantly more shear-responsive genes per total number of genes. The distribution of shear-responsive genes per total basepairs DNA was 1.97e-8$\pm$1.00e-8. Chromosomes 17 (4.70e-4) contained higher frequency shear-responsive gene per DNA length at the 95% C.I. level, as well as chromosomes 19 (3.44e-7) and 22 (3.03e-7) at the 68% C.I. level.

6.3.6 Cellular and functional distribution of conserved shear-responsive molecules

GenBank Accession numbers for the set of conserved shear-responsive genes (574 original probe names, minus 37 probes without GenBank Accession numbers) were analyzed using Ingenuity Pathways Analysis. The resulting signaling network of 738 genes was categorized according to cellular location (Figure 37A) or molecular function (Figure 37B). Molecules in this network were primarily found in the nucleus (28%) or cytoplasm (25%). Molecules associated with the plasma membrane or extracellular space accounted for 12% or 9% of the set, respectively. Molecular functions associated with the shear-responsive signaling network included enzymes (15%), transcription regulators and group molecules (9%), complexes (7%), and peptidases and kinases (5%). Translation regulators, ligand-dependent nuclear receptors, ion channels, endogenous mammalian chemicals, transmembrane receptors, microRNAs, growth factors, and cytokines were represented at 1% or less. This analysis could not be completed for all 738 molecules in the signaling network, since many were not associated with either a cellular location (26%) or molecular function (37%).

6.3.7 Direct interactions within conserved shear-responsive gene set

IPA analysis identified the most likely 25 signaling networks based on grouping the 574 conserved shear-responsive probes using both direct and indirect connections. To specifically highlight direct connections between shear-responsive genes, 370 interactions within the ‘conserved’ set were determined using GeneSpring signaling pathway analysis. Molecules with direct interactions within the set grouped into two initial categories: the majority were

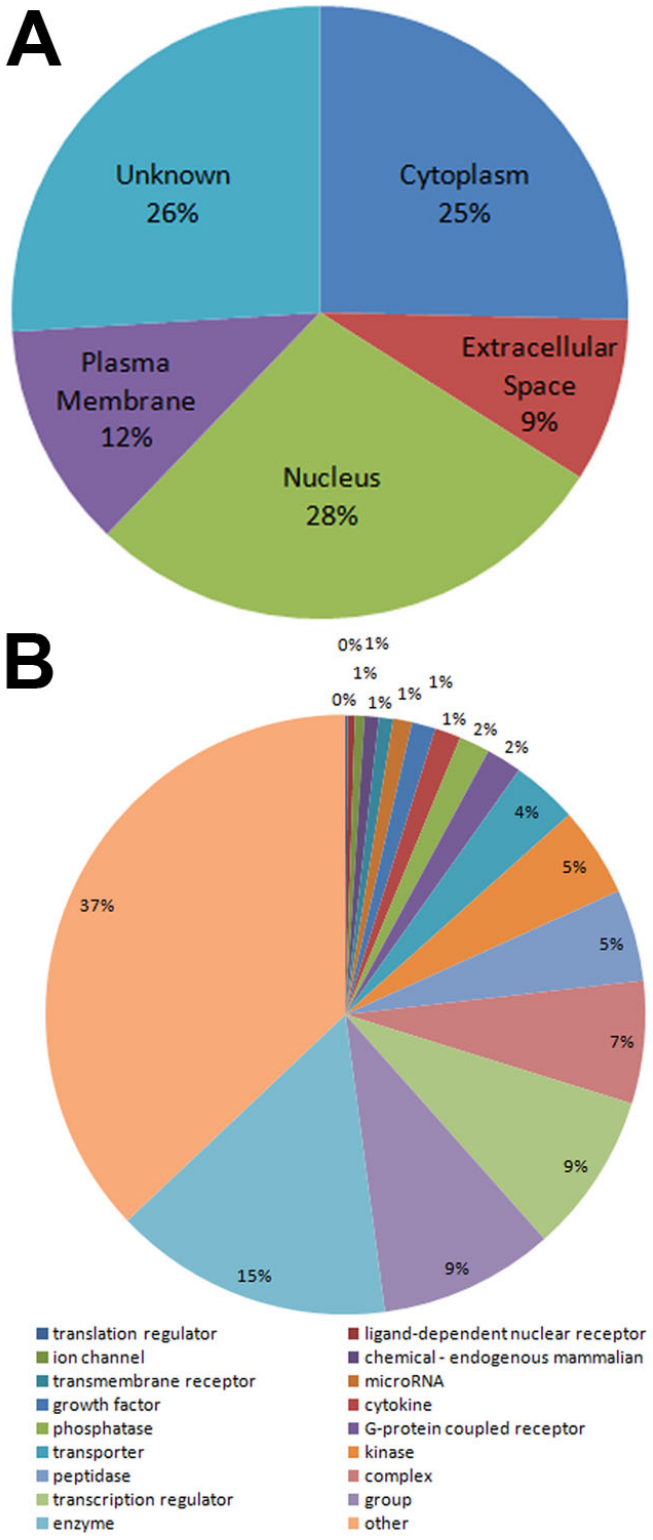


Figure 37: Cellular locations and molecular functions associated with conserved shear stress-responsive signaling network. A signaling network comprised of 785 molecules was generated using IPA software analysis of the set of conserved, shear-responsive genes (574 microarray probes). (A) Cellular location distribution of molecules in shear-responsive signaling network. (B) Functions associated with molecules in shear-responsive signaling network.

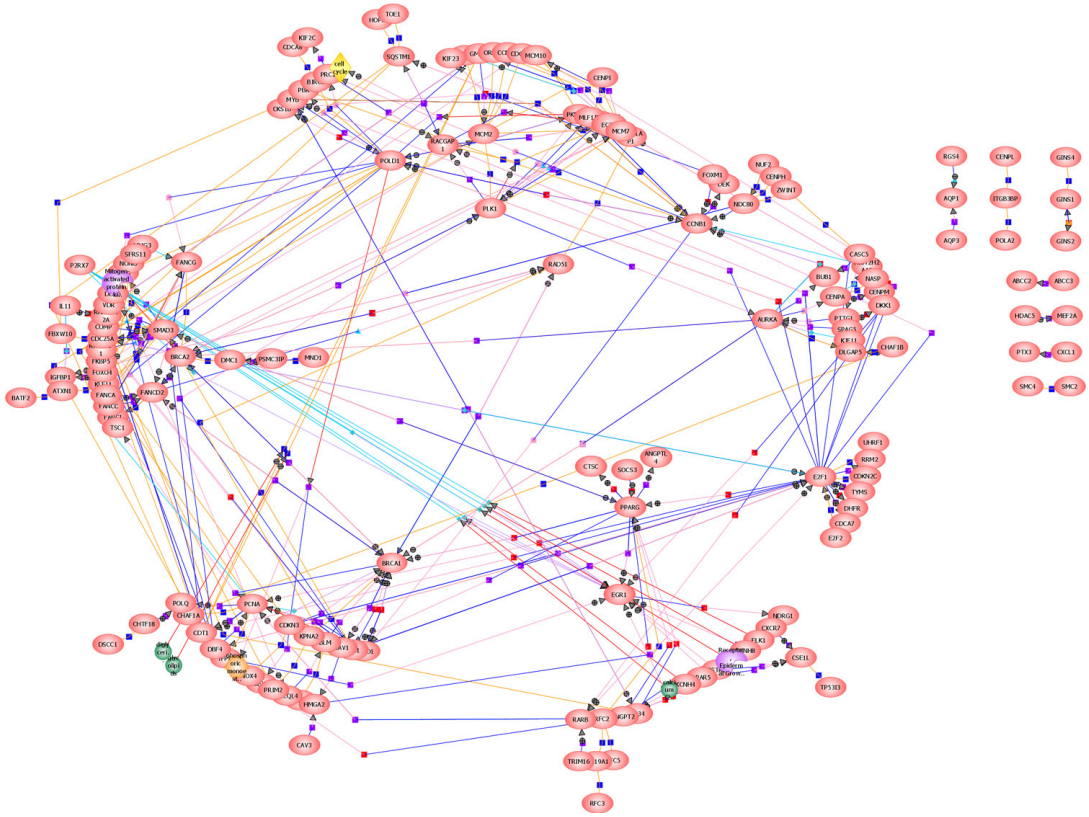


Figure 38: Direct signaling interactions between conserved shear-responsive genes. Gene Spring software analysis determines signaling pathways based on the set of 574 conserved shear-responsive genes ($p < 0.05$ for both ECs and MSCs paired t-tests; $p < 0.05$ for force-dependent expression based on ANOVA). Unconnected molecules are not shown.

connected in a single, multicomponent network (Figure 38, left) while a minority of genes were connected as isolated pairs or trios (Figure 38, right). Molecules in the large direct interaction network can be described by a local connectivity score, proportional to the number of connections a node has within the shear-responsive set. Seven distinct 'hour-glass' motifs appear in this interaction network. This suggests a subset of molecules act may as convergence points for shear-responsive signaling and affect the shear-response of multiple downstream targets. These convergence nodes include: AURKA, BRCA1, BRCA2, CNB1, E2F1, EGR1, FANCD2, FANCG, MCM2, PLK1, POLD1, PPARG, and SMAD3.

6.3.8 Molecular function clusters affected by conserved shear stress-responsive genes

Two Gene Ontology (GO)-based analysis methods were employed to determine molecular functions enriched in the set of conserved shear-responsive genes: GeneSpring software and functional clustering analysis with the Database for Annotation, Visualization, and Integrated Discovery (DAVID) tool. GO analysis in GeneSpring identified 30 functions significantly (corrected p-value< 0.05) enriched in the conserved shear-responsive set, with two additional functions identified by relaxing the significance cut-off to $p < 0.10$ (Table 11). These functions relate to different aspects of cell proliferation: cell cycle, DNA replication, mitosis, chromosome maintenance and function ($p \leq 0.001$). Few significantly-altered functions affect processes unrelated to proliferation: non-membrane-bounded organelles (p=0.004), organelle organization and biogenesis (p=0.062), and nucleic acid metabolism (p=0.074).

Gene ontology analysis using the DAVID tool confirmed the enrichment of cell cycle- and DNA replication-related functions seen with GeneSpring analysis. Functional clustering in DAVID clusters shear-responsive genes according to common associated functions (i.e., GO terms), based on a calculated kappa score and subsequent fuzzy heuristic clustering algorithm. 28 functional clusters with significant ($p < 0.05$) median values were identified (Table 12). DAVID functional clusters related to cell proliferation include DNA replication (clusters 1, 10, 12, 14-15, 20, 22, and 24), cell cycle (2, 8, 17, and 28), spindles

and chromosomes (4, 6, 9, 15, 18-19, and 26), DNA damage and repair (3 and 11), and nucleus and membrane-bound organelles (5). DAVID functional clustering identified other functions enriched in the set of conserved shear-responsive genes relative to the whole genome background set: BRCA1 signaling (7 and 29), anatomical structure development (21), nucleotide binding (13), kinase activity (27), and GTPase/enzyme regulator activity (25).

6.3.9 Predicted transcription factor regulators of conserved shear-responsive genes

Computational Ascertainment of Regulatory Relationships (Inferred from Expression) (CARRIE) is an online tool enabling prediction of the transcription regulatory network affected by microarray analysis of two different groups. Analysis of promoter regions is based on GenBank Accession identifiers and their associated fold change ($|FC| \geq 3.0$) and p-values ($p < 0.01$), resulting in separate analysis for MSCs and ECs with the same set of GenBank Accession numbers. Transcription factors and their predicted significance change between microarray conditions ($p < 0.05$ for at least one cell type) are listed for MSCs and ECs in Table 13. More transcription factors are significantly associated with ECs shear-response than MSCs shear-response (139 vs. 75). 26 transcription factors were identified in both cell types, representing 34% or 19% of the total number of significant transcription factors in MSCs and ECs respectively.

6.4 Discussion

This study provides a snapshot of MSCs transcriptome changes due to vascular-relevant fluid shear stress, in comparison to ECs shear-responsive signaling. Similarly to ECs, MSCs respond to steady laminar shear stress on fibronectin-coated glass with changes in gene expression detectable within 24 hours. However, unlike ECs, changes in gene expression in MSCs do not correlate with realignment parallel to the direction of applied fluid flow. Whole human genome microarray analysis demonstrates signaling profiles can be grouped according to cell type and force condition. MSCs gene expression changes due

to shear stress are fewer in number, magnitude fold change, and significance range compared to ECs. In spite of marked differences between MSCs andECs, a statistical approach identified a set of genes whose gene expression is significantly ($p < 0.05$) force-dependent in both cell types. Ontological assessment of conserved shear-responsive genes shows (a) uneven chromosomal distribution, (b) enrichment of particular cellular locations (cytoplasm and nucleus) and molecular functions (enzymes), and (c) marked upregulation of cell cycle and DNA replication-related signaling networks. This analysis predicts specific molecules, either convergence nodes in a direct interaction model or transcription factors, that may account for multiple aspects of the observed shear-responsive gene changes.

This comparison of shear stress between ECs and MSCs is biased by focusing on gene expression at a single timepoint, single applied shear stress profile (magnitude, frequency), and on a single underlying protein substrate. Additional information about cellular response to shear stress would be gained by repeating these studies and varying the above shear stress parameters or assessing signaling changes at chromosomal, miRNA, protein, or post-translational modification levels. Use of publically available tools for ontology analysis (e.g., GeneSpring, IPA, DAVID, and CARRIE) is convenient, but means that customized analyses, with transparent algorithms and known assumptions, are rarely available. Since biases resulting from each analysis method are inherent in the result, multiple methods were used when possible to triangulate on reproducible themes (e.g., cell cycle regulation due to shear stress). Finally, conclusions drawn from this work would be strengthened by additional, single factor experiments to test these hypotheses.

Small regions of ECs, but not MSCs, align parallel to the direction of applied shear stress (15 dyn/cm^2) within 24 hours (Figure 31). This difference in cellular response to shear stress may be related to differences in cell type morphology, specifically cell-cell and cell-matrix connections [272, 104, 67]. MSCs occupy more surface area than ECs. More gaps are present between spindle-shaped MSCs compared to the close-packed arrangement of cobblestone-shaped ECs. Decreased alignment in MSCs compared to ECs is consistent if remodeling occurs proportional to a balance between applied force and the net force of cell-matrix attachment and/or coordination through direct cell contact mechanisms

[272]. Other reports state that MSCs reorient in response to other types of mechanical cues (e.g., applied cyclic strain [148] or combined pulsatile pressure, radial distension, and shear stress [205]). This difference in MSCs remodeling following applied force may relate to differences in initial cell density or matrix presentation (e.g., monolayer vs. 3-D gel) that affect cell-cell and cell-matrix connections or to regulatory mechanisms that distinguish between force type. Longer duration applied shear stress studies could also determine whether MSCs undergo realignment to shear stress at a slower rate than ECs.

Although morphology of MSCs exposed to shear stress or static culture did not visibly differ, samples can be distinguished from one another using principle component analysis. Transcriptome profiles differ more between cell types than force condition, verified by both greater separation on the PCA plot and expression of more genes dependent on cell type than force condition based on two-factor ANOVA. Principal component 2 values decrease in response to shear stress for both MSCs and ECs, but application of shear stress does not shift MSCs samples towards ECs values (principal component 1). This suggests qualitatively that MSCs and ECs share similar responses to applied shear stress, but that 24 hours applied shear stress is not sufficient to induce endothelial-like signaling in MSCs.

ECs have greater average magnitude expression change in response to shear stress (Figure 25) and three times as many shear-responsive genes at low ($p < 0.05$, n=3 and $|FC| > 1.5$) (Figure 26). This trend is exaggerated at more stringent shear-response cut-offs, with more than eight times as many highly significant ($p < 0.001$, n=3) shear-responsive genes in ECs as MSCs. ECs may be more sensitive to shear stress than MSCs because shear-response is an essential feature of endothelial function, not necessarily MSCs. Innate mechanosensitivity of MSCs and other stem cells has been shown to promote differentiation along specific lineages [71, 192, 136]. More recent work suggests mechanosensitivity of MSCs may also develop as a function of differentiation, based on responses of MSCs-like dental pulp cells differentiated along osteogenic lineages [142]. Additional studies, possibly including longer duration applied shear stress and inclusion of intermediate cell types between undifferentiated MSCs and differentiated ECs, are needed to determine the cause of mechanosensitivity differences observed in these studies.

Genes whose expression was significantly force-responsive according to two-factor ANOVA and changed significantly in both ECs and MSCs by at least 1.5-fold were defined as 'conserved' shear-responsive genes. 574 genes, approximately 1% of the total number assessed, met this criteria for significance cut-off of $p < 0.05$. When paired t-test significance thresholds were increased to $p < 0.01$, no genes were conserved in both cell types. However, 55 and 462 genes were highly conserved in either MSCs or ECs respectively. Highly conserved mechanorepsonses present in only one cell type suggest that different signaling networks are activated in each cell type in response to mechanical force.

Conserved shear-responsive molecules are located primarily in the nucleus and cytoplasm. Identification of fewer molecules associated with the plasma membrane and extracellular space may be because these experiments focused exclusively on gene expression changes. This could be because shear-responsive changes at locations further from the nucleus occur at the protein or post-transcriptional level. Cellular location analysis highlights a limitation of current ontology software: the inability to classify the cellular location of 26% of conserved shear-responsive genes limits the strength of conclusions drawn. Molecular functions primarily associated with conserved shear-responses are enzymes, transcription regulators, group, and complex molecules. Group molecules are those representing a set with similar function (protein family, same function in signaling pathway, same enzymatic activity). Complex molecules refer to multiprotein units comprised of multiple genes. As with cellular location, this functional analysis is limited by the inability to classify 37% of molecules within the pre-defined set of 17 functional categories. Expression of signaling molecules can be regulated at many different stages from transcription through degradation [2]. Enrichment of gene expression regulation in specific cellular locations or molecular functions could indicate an advantage of this level of regulation relative to other modes. Such an advantage could be in terms of signaling or spatial efficiency, kinetics of response, or metabolic demands [303]. Additional studies are necessary to test this generalization.

This analysis of 'conserved' shear-responsive genes does not distinguish between genes each independently force-sensitive or the downstream effectors of a few signaling

nodes that amplify the initial force response. To explore this concept, signaling networks generated in GeneSpring using direct only or combined direct and indirect connections were compared. Direct interaction analysis of conserved shear-responsive genes identified here highlights a signaling pathway containing 134 molecules connected by one or more links to one another (Figure 38). The presence of multiple hourglass motifs suggests a small subset of genes may account for a much larger number of observed signaling changes. Manipulating the expression or activity levels of these 13 identified convergence nodes and assessing the subsequent shear-responses of linked molecules could be used to determine the importance of the convergence nodes in shear stress response. All 13 convergence nodes affect DNA replication, cell cycle, and DNA repair functions, as determined via GO biological process annotations. This redundancy in functional control underscores the importance of cell proliferation and cell cycle regulation via shear stress. This data demonstrate shear stress regulates cell proliferation in multiple cell types, not only ECs.

Mechanoresponses may be regulated by both signaling networks and genome organization. Shear-responsive genes are not distributed uniformly across chromosomes, genes, or DNA length. The increase in shear-responsive genes on Chromosome 1 is likely because this chromosome is larger than the others. Chromosomes 4 and 11 have increased shear-responsive genes per chromosome and per total number of genes on the chromosome. Future analysis could determine if these genes correlate with a particular region of the chromosome or share sequence or regulatory similarities. Chromosome 17 falls outside the 68% confidence interval for shear-responsive genes per chromosome and the 95% confidence interval for genes per base pair. Chromosome 17 is not significant in terms of shear-responsive genes/total genes. This suggests that non-coding regions, such as cis-regulatory regions or miRNAs, may be involved in increased shear-sensitivity of Chromosome 17. Chromosomes 2, 18, 19, 21, and 22 fall outside the lower confidence internal bounds (65%) of only one of three analysis methods (chromosome, total genes, length). Collectively, this analysis suggests chromosomes 4, 11, and 17 may have force-sensitivity properties meriting future investigation, in contrast to chromosomes responsive

at lower confidence levels (2,18,29,21,22) or of unusually large size (1).

Results of this mechanosignaling analysis are likely biased by two experimental constraints: underlying protein adhesion mechanism and media type [104, 67, 272]. Cells were coated on fibronectin for these studies, to avoid the cellular remodeling observed in MSCs in response to shear stress on Type I Collagen-coated surfaces. Since cell-matrix attachment mechanisms alter both signaling and adhesion strength, though, the underlying protein coating likely affects the specific signaling response triggered by mechanical force. Comparison of shear stress signaling responses in the same cell type on different protein substrates would determine these effects. The second factor inherently biasing the specific mechanosignaling response observed is due to differences in media type (ECs or MSCs). To isolate the signaling effects due to mechanical forces, ECs and MSCs were cultured and exposed to applied force using standard growth media recommended for each cell type. These media formulations differ in basal media (MCDB-131 vs. MSCs Basal Media), growth factors, and serum. However, if mechanosignaling changes depend on the initial culture media signaling environment, then these changes would appear in the analysis as cell type-specific mechanosignals. Normalizing the biochemical cues presented to each cell type may identify additional conserved shear-responses that were masked by the experimental design used in this study.

6.5 Conclusions

This work demonstrates that ECs and MSCs have markedly different morphology and gene expression responses to applied shear stress in terms of the number, magnitude, and significance of expression level change. Separation of samples using PCA indicates characteristic profiles can be used to separate cell types and applied shear conditions for this 2x2 comparison; future studies are needed to define these profiles and potentially generalize this method across a broader range of cell types or force conditions. Cell cycle, proliferation, and DNA replication are significantly shear-responsive. Future studies may determine the evolutionary importance of this function, as well as the extent of mechanoregulation of cell proliferation across other cell types and species. Finally, this work demonstrates that

signaling changes can be triggered by applied mechanical cues, even in the absence of visible morphological differences.

6.6 Materials and Methods

Supplies Cells and culture media were purchased from Lonza. Microarrays and associated materials were purchased from Agilent. Standard qPCR reagents were purchased from Qiagen (RNA isolation), Invitrogen (cDNA synthesis), and ABI (qPCR mastermix).

Cell culture of MSCs &ECs Human adult bone marrow-derived mesenchymal stem cells and aortic endothelial cells were cultured according to manufacturer's recommendations (Lonza). MSCs were expanded to Passage 6 and characterized for expression of protein surface markers and differentiation potential along osteogenic, chondrogenic, and adipogenic lineages prior to experimental use. ECs expanded to Passage 5 were used for experiments.

Applied shear stress Steady laminar fluid shear stress was applied using a parallel plate shear system [155]. Cells were seeded on fibronectin-coated glass slides at 10,000 cells/cm^2, calculated using a Coulter Counter Multisizer 3 (Beckman Coulter). Cells were allowed to attach for two days prior to application of shear stress (5 or 15 dyn/cm^2) or parallel static culture for up to 48 hours. Cell morphology was determined with phase microscopy (Axiovert microscope, Zeiss) immediately prior to and following exposure to mechanical force.

Microarray sample preparation To minimize noise due to biological and experimental variability, cell lysates were pooled from four independent samples per static or applied strain replicate. Three independent experiments were completed per cell type. RNA was isolated according to manufacturer's protocols (Qiagen). All samples passed two levels of quality control: first, the concentration, $A_{\frac{260}{280}}$, and $A_{\frac{260}{230}}$ were measured using a Nanodrop (Thermo Scientific) and second, the RNA integrity number (RIN) was determined using a Bioanalyzer (Agilent). cDNA synthesized from high quality RNA samples was labeled for one-color detection and run on a whole human genome 60-mer microarray (Agilent), four arrays per slide. Microarray images were captured using Feature Extraction software and

passed manufacturer-recommended quality control metrics for image uniformity.

Microarray data analysis Feature Extraction data was imported into Gene Spring 10.0 for normalization and statistical assessment. 12 of 12 arrays passed quality control metrics within GeneSpring, enabling three replicates per group to be analyzed. Genes were filtered to ensure present or marginal expression levels in at least one sample. ANOVA with Benjamini-Hochberg multiple testing correction was applied to all sample groups determined whether gene expression depended significantly on cell type or force condition. Since an independent experiment yielded two microarray samples (one pooled shear sample and one pooled static sample), paired data analysis was used to compare static and shear samples. P-values from two-tailed paired t-tests ($p < 0.05$) and paired fold change cut-off thresholds ($|FC| > 1.5$) defined genes significantly altered in either ECs or MSCs. No genes met significance criteria in MSCs when multiple testing corrections were applied. Thus, MTC were not used for either cell type, in order that final lists of shear-responsive genes could be compared between cell types based on the same numerical analysis method. Conserved strain-responsive genes were defined as those meeting three criteria: two-way ANOVA significant dependence on applied force ($p < 0.05$), ECs paired t-test significant difference between static and applied strain groups ($p < 0.05$) with fold change $\geq$1.5, and MSCs paired t-test significant differences ($p < 0.05$) with fold change $\geq$1.5.

Ontological analysis of microarray results Functional, regulatory, and subcellular location analysis of strain-responsive genes was completed using Ingenuity Pathways Analysis (Ingenuity), the Database for Annotation, Visualization and Integrated Discovery (DAVID) 2008 [107, 64], and the Computational Ascertainment of Regulatory Relationships (Inferred from Expression) (CARRIE) software [93, 94]. For IPA analysis, GenBank Accession Numbers for the set of conserved force-responsive molecules were uploaded as a data set and analyzed for core analysis using direct and indirect relationships, endogenous chemicals, and up to 25 networks per analysis, each with up to 35 molecules. Descriptions for each molecule associated with the resulting 25 networks of direct and

indirect interactions were exported from IPA into MS Excel and sorted according to molecular function or subcellular location. GenBank accession numbers for conserved force-responsive probes were uploaded to the DAVID interface as the gene list and compared to the Homo sapiens background gene list. Functional annotation clustering was performed via DAVID version 6.7b and results exported to MS Excel for table formatting. Both IPA and DAVID analysis relied only on GenBank Accession numbers. For prediction of transcriptional regulators, both GenBank Accession numbers, as well as fold change and p-values, were uploaded for each cell type. Pre-processed array data in this format were uploaded and analyzed using the TRANSFAC Human matrix list and HG-U133 promoter list. Parameter setttings used for conserved force-responsive molecules in this analysis were: significant expression change defined as $|FC| \geq 3.0$ and significance ($p < 0.01$). Significant transcription factors were defined using default cutoffs for frequency of significant sites in random promoters ($p_{random} < 0.001$) and binding site overabundance in one promoter ($p_{overabund} < 0.01$). Finally, chromosomal location analysis was completed by sorting data output from GeneSpring for the conserved set of force-responsive probes. Reference information on length and content of chromosomes was obtained from the Vega Genome Browser.

Standard qPCR assessment Individual genes were assessed using standard qPCR. RNA was isolated from kinetic experiments and quantified as above. cDNA was synthesized using a FirstStrand III SuperScript Kit (Invitrogen) and prepared for qPCR with custom designed primers (Primer Express 3 software; Invitrogen custom primer synthesis; ABI SYBR mastermix). qPCR samples were run on a StepOne Plus machine (ABI) and baseline-subtracted C_t analyzed in Excel (Microsoft). Data were converted to molar concentrations using a standard curve and normalized to Gapdh expression. Fold-changes were calculated as the ratio of applied shear/static relative expression. A 1.5-fold change threshold was used to identify shear-responsive genes. Fold changes calculated from microarray or qPCR data were compared.

Statistical analysis Microarray data were analyzed with two-factor ANOVA and paired t-test. Functional significance was determined using statistical methods inherent in IPA,

DAVID, or CARRIE, respectively. qPCR data was analyzed in MS Excel with two-tailed paired t-tests. Experimental design was employed to minimize the effect of biological variability (i.e., 4 pooled samples per microarray) and randomize the effect of experimental variability (n$\geq$3 independent experiments/comparison). Significance cut-offs, defined explicitly throughout the text, were at maximum $p < 0.05$.

6.7 Acknowledgements

We are grateful to Leonard Anderson and Michelle Leander at the Morehouse School of Medicine core facility for help running microarrays and preliminary microarray analysis.

Table 11: Gene Ontology (GO) terms relatively upregulated in conserved shear-responsive genes. Gene Spring software analysis of 32 significant ($p < 0.10$) molecular functions, cellular components, and biological processes based on the Gene Ontology database. For highly conserved shear-responsive genes (list of 574 genes), only 2 GO terms are significant ($p < 0.10$): DNA metabolic process and DNA replication.

GO Term	Corrected p-value
cell cycle	0.000
DNA metabolic process	0.000
DNA replication	0.000
cell cycle phase	0.000
mitotic cell cycle	0.000
cell cycle process	0.000
chromosomal part	0.000
chromosome	0.000
M Phase	0.000
chromosome, centromeric region	0.000
mitosis	0.000
M phase of mitotic cell cycle	0.000
cell division	0.000
chromosome segregation	0.000
replication fork	0.000
regulation of cell cycle	0.000
nucleus	0.000
DNA repair	0.000
response to DNA damage stimulus	0.000
mitotic sister chromatid segregation	0.000
sister chromatid segregation	0.000
spindle organization and biogenesis	0.000
DNA-dependent DNA replication	0.001
chromosome organization and biogenesis	0.003
non-membrane-bounded organelle	0.004
intracellular non-membrane-bounded organelle	0.004
cell cycle checkpoint	0.006
DNA replication initiation	0.007
alpha DNA polymerase: primase complex	0.016
DNA replication factor C complex	0.047
organelle organization and biogenesis	0.062
nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	0.074

Table 12: Functional clusters significantly ($p < 0.05$) affected by conserved shear-responsive genes. DAVID analysis of the set of 574 conserved shear-responsive probes identified 28 functional clusters. General functions and associated conserved shear-responsive genes areas listed in order of decreasing significance.

Clustering Group	Associated Function	Median	Associated Genes
2	DNA replication	1.13E-19	NM_182802, NM_000057, NM_181471, NM_182776, NM_172164, NM_001034, NM_014321, NM_181578, NM_021067, NM_002915, NM_001033, NM_003504, NM_002691, NM_030928, NM_005483, NM_005914, NM_000947, NM_002592, NM_005441, NM_004526, NM_002689, NM_016095, NM_016937, NM_182751, NM_000946, NM_002692, NM_001018115, NM_002266, NM_004260, NM_001003395, NM_004219, NR_002734, NM_001809, NM_006607, NM_006716, NM_003686, NM_001015053, NM_012117, NM_000059, NM_018193, AK056691, NM_006479, NM_000136, NM_002993, NM_013282, NM_182625, NM_003516, NM_001017420, NM_003579, NM_018063, NM_133330, NM_133336, NM_002875, NM_003483, NM_006444, NM_004111, NM_002895, NM_183404, NM_003609, NM_007295, NM_006397, NM_015895, NM_004629, NM_005496, NM_007068, NM_000135, NM_001071, NM_199420, NM_057749
1	cell cycle and cell division	4.06E-19	NM_001018115, NM_001789, NM_002266, NM_144665, NM_004464, NM_001003395, NM_004219, NM_001005414, NM_018492, NM_006716, NM_003686, NM_015341, NM_018136, NM_001015053, NM_001012409, NM_001012410, NM_005938, NM_000059, NM_018193, NM_005192, NM_022346, AK056691, NM_080668, NM_182908, NM_031966, NM_003981, NM_013282, NM_012291, NM_001017420, NM_030928, NM_003579, NM_145697, NM_005483, NM_138375, NM_001826, NM_005441, NM_000465, NM_004526, NM_024808, NM_018063, NM_152562, NM_001262, NM_016937, NM_004701, NM_001946, NM_002875, NM_003920, NM_006444, NM_005030, NM_182802, NM_018101, NM_019885, NM_182776, NM_172164, NM_002895, NM_183404, NM_003318, NM_005225, NM_007295, NM_018365, NM_015714, NM_016323, NM_020242, NM_015895, NM_006101, NM_198433, NM_004629, NM_005496, NM_005429, NM_001012271, NM_003504, NM_002691, NM_182687, NM_004091, NM_014750, NM_006845, NM_018204, NM_004523, NM_007068, NM_007174, NM_152524, NM_002592, NM_005375, NM_057749, NM_006461, NM_004336, NM_000189, NM_013277
4	DNA damage and repair	2.05E-08	NM_001018115, NM_003920, NM_004260, NM_000057, NM_004219, NM_182776, NM_004111, NM_181578, NM_003686, NM_002915, NM_007295, NM_005938, NM_018193, NM_000059, NM_004629, NM_006479, NM_000136, NM_013282, NM_182625, NM_002691, NM_001017420, NM_002133, NM_003579, NM_005483, NM_002592, NM_005441, NM_000135, NM_000465, NM_001071, NM_199420, NM_016937, NM_002692, NM_002875, NM_002395, NM_174936, NM_007034, NM_000641, NM_001015053, NM_016931, NM_002852, NM_003900, NM_153020, NM_002993, AK096148, NM_012072, NM_000185, CB243784, NM_006528, NM_080725, NM_139314, NM_018948, NM_002061, NM_014278, NM_001511, NM_005410, NM_032784, NM_213633, NM_148170, NM_001814, NM_006096, NM_138711, NM_015967, NM_006187, NM_000433, NM_020169, NM_003835, NM_002359, NM_033092, NM_001049, NM_000266, NM_001964, U68019, NM_005902, NM_000332
3	chromosomal part	8.28E-08	NM_001018115, NM_003483, NM_003920, NM_006444, NM_003724, NM_024629, NM_007280, NM_018101, NM_000057, NM_181471, NM_182776, NM_001005414, NM_001809, NM_014321, NM_002359, NM_181578, NM_001002876, NM_012117, NM_002915, NM_022909, NM_007295, NM_001012409, NM_001012410, NM_018193, NM_001012267, NM_006101, NM_080668, NM_005496, NM_001012271, NM_014288, NM_003516, NM_030928, NM_145697, NM_006845, NM_033319, NM_006733, NM_007068, NM_000947, NM_152524, NM_002592, NM_002689, NM_004526, NM_018063, NM_014729, NM_016937, NM_018132, NM_004336, NM_000946, NM_002875, NM_024491, NM_018424, NM_004411, NM_000037, NM_005893, NM_000059, NM_052969, NM_031966, NM_003981, NM_012291, NM_002133, NM_007018, NM_004701, NM_005030, NM_015000, NM_003318, NM_021992, NM_015569, NM_020242, NM_198433, NM_004430, NM_031217, NM_014750, NM_145654, NM_014021, NM_007068, U68019, NM_005902, NM_020394, NM_199420, NM_057749, NM_016095, NM_030941, NM_018132, NM_004336, NM_000946, NM_001015053, NM_016931, NM_032564, NM_006918, NM_015697, NM_001361, NM_005441, NM_000465, NM_019885, NM_178858, NM_198540, NM_001490, AK091439, NM_018087, NM_004091, BC021898, NM_001753, U68019, NM_005902, NM_199420, NM_000189, NM_002266, NM_00107973, NM_005483, BC048985, NM_003979, AK027315, NM_002895, NM_183404, CB243784, NM_005225, BC009364, NM_001316, NM_006467, NM_018371, NM_182687, NM_004737, NM_002883, NM_013445, NM_005375, NM_153485, NM_000332
5	nucleus and intracellular membrane-bound organelle	5.84E-06	NM_001005463, NM_017769, AK096342, NM_144665, NM_004260, NM_181471, NM_001809, NM_033661, NM_003597, NM_202002, NM_014321, NM_181578, NM_018136, NM_001002876, NM_001015053, NM_006096, NM_016931, NM_005938, NM_000059, NM_018193, NM_003900, NM_022346, AK056691, NM_080668, NM_031966, NM_138456, NM_000136, NM_003981, NM_014288, NM_013282, NM_012291, NM_003516, NM_001017420, NM_030928, NM_007018, NM_033319, NM_005441, NM_003384, NM_004526, NM_000465, NM_001262, NM_133330, NM_133336, NM_016937, NM_004701, NM_002875, NM_004118, NM_003920, NM_024629, NM_005030, NM_007280, NM_018101, NM_000057, NM_182776, NM_172164, NM_017613, NM_004111, NM_002359, NM_007295, NM_018365, NM_001012267, NM_006101, NM_014079, NM_001012271, AK091439, NM_018087, NM_002691, NM_004091, NM_170589, NM_003472, NM_014750, NM_145654, NM_014021, NM_007068, U68019, NM_005902, NM_020394, NM_199420, NM_057749, NM_016095, NM_030941, NM_018132, NM_004336, NM_000946, NM_153618, NM_182751, NM_013277, NM_001018115, NM_002266, NM_003724, NM_031942, NM_002315, NM_004219, NR_002734, NM_001005414, AI085037, NM_182964, NM_018719, NM_006607, NM_006716, NM_003686, NM_015341, NM_012117, NM_021067, NM_138711, NM_001012409, NM_001012410, NM_004420, NM_017915, NM_139211, NM_153020, NM_001017535, NM_000965, NM_182908, NM_006479, BC004543, NM_182625, NM_014583, NM_002133, NM_003579, NM_145697, NM_005483, NM_138375, NM_005914, BC048985, NM_000947, AL117578, NM_002689, NM_018063, NM_152562, NM_006993, NM_175623, NM_002692, NM_003483, NM_005985, NM_006444, NM_001012507, AK027315, NM_182802, NM_018664, NM_005587, NM_002895, NM_183404, NM_005225, NM_007257, NM_003609, NM_002915, NM_022909, NM_006397, BC009364, NM_015895, NM_002448, NM_198433, CD619445, NM_004629, NM_005496, NM_007177, NM_006467, NM_001316, NM_003504, NM_004117, NM_001964, NM_014278, NM_002883, NM_006845, NM_201629, NM_004817, NM_006733, NM_006561, NM_017826, NM_152524, NM_002592, NM_000135, NM_005375, NM_014729, NM_153485, NM_000332, NM_000037, NM_148170, NM_001814, NM_032564, NM_001361, NM_014905, NM_007193, NM_178858, NM_001490, NM_018361, NM_023004, BC021898, NM_001753, NM_002579, NM_174936, NM_001017973, AK096148, NM_000433, NM_003979, NM_018371, NM_004737, NM_013445, NM_001234, NM_000691, NM_006918, NM_015697, NM_019885, NM_198540, AL713762, NM_139241, NM_144492, NM_000189, NM_012072, CB243784, NM_182687, NM_012393, NM_004808, NM_015967, NM_020169, NM_145014, NM_015000, NM_002395, NM_021992, NM_020242, NM_018948, AF339799, NM_031217, NM_013432, NM_004523, NM_018424, NM_174858, NM_001003395, NM_032636, NM_006470, NM_033092, NM_015569, NM_017644, NM_013296, NM_024430, NM_004657, NM_018204, NM_006461, NM_005480, AK074050, NM_024491, NM_133459, NM_005893, NM_001946, NM_080725, NM_006895, NM_002061, NM_001846, NM_015148, NM_005781, NM_004411, NM_001034, NM_052969, NM_001033, NM_001845, NM_000221, NM_014791, NM_003318, NM_016323, AK074711, NM_005202, NM_007174, NM_006755, NM_014783, NM_153332, NM_001789, AF334184, NM_015310, NM_133489, NM_018098, NM_032818, NM_000392, NM_005602, NM_012242, AK125261, NM_015008, NM_006495, NM_006143, NM_002402, NM_020311, NM_018286, NM_003786, NM_199329, NM_024522, NM_002210, NM_002589, NM_213633, NM_198098, NM_020182, NM_032814, NM_006727, NM_003834, NM_003835, NM_014331, NM_153487, NM_052839, AY358366, NM_013390, NM_012339, NM_004753, NM_00103620, NM_000891, NM_000723, NM_018224, NM_006187, NM_032148, NM_020766, NM_001773, NM_194255, NM_152372, NM_024660, NM_001049, NM_005429, NM_181078, NM_004734, NM_002562, NM_001003927, NM_013982, NM_173808, NM_032420, NM_153377, NM_005397, NM_020400, NM_021012, NM_004955, AK025855, CX165016, NM_020949, NM_032961, NM_015257, NM_004925, NM_014399
7	BRCA1 signaling	5.88E-05	NM_001018115, NM_000136, NM_000135, NM_007295, NM_000465, NM_004629, NM_000059, NM_002875
11	DNA recombination and repair	9.68E-05	NM_007295, NM_000059, NM_003579, NM_002875, NM_006479, NM_004111, NM_016937, NM_003686, NM_002266, NM_007068, NM_004260, NM_000057
8	cell cycle checkpoint	1.37E-04	NM_001012271, NM_003504, NM_007295, NM_005938, NM_057749, NM_030928, NM_000059, NM_001005414, NM_004336, NM_003318, NM_004629, NM_012291, NM_182687, NM_014750
6	chromosome condensation	1.64E-04	NM_006444, NM_004260, NM_012291, NM_004219, NM_001005414, NM_014750, NM_145697, NM_015341, NM_152524, NM_007295, NM_001012409, NM_001012410, NM_006101, NM_080668, NM_022346, NM_005496
10	DNA transcription	1.80E-04	NM_000947, NM_002592, NM_000057, NM_002915, NM_002689, NM_181471, NM_182776, NM_030928, NM_016937, NM_000946, NM_181578, NM_003920, NM_006444, NM_007068, NM_012117, NM_004526, NM_014321, NM_002875, NM_002691, NM_199420, NM_002692, NM_006467, NM_001071, NM_001361, NM_001034, NM_001033, NM_012393, NM_174858, NM_006452, NM_002765, NM_018945, NM_002993, NM_006187
9	spindle organization	2.72E-04	NM_004523, NM_003981, NM_001005414, NM_006461, NM_006101, NM_003318, NM_198433, NM_001012271, NM_014750, NM_004336, NM_013277
17	meiosis	6.83E-04	NM_003686, NM_007068, NM_019885, NM_001012409, NM_001012410, NM_018365, NM_000059, NM_003579, NM_002875, NM_002266, NM_004260, NM_000057, NM_007295, NM_006479
12	DNA replication initiation	9.57E-04	NM_005914, NM_007068, NM_182802, NM_000057, NM_002915, NM_004526, NM_181471, NM_182776, NM_002875, NM_181578, NM_003504, NM_057749, NM_030928, NM_016937, NM_002689
15	spindle organization & microtubules	1.47E-03	NM_004523, NM_003981, NM_001005414, NM_006461, NM_006101, NM_003318, NM_198433, NM_001012271, NM_024491, NM_005030, NM_004411, NM_012291, NM_014750, NM_031217, NM_007018, NM_006845, NM_018204, NM_007295, NM_000059, NM_015569, NM_020242, NM_004336, NM_004701, NM_013277, NM_031966, NM_002266, NM_005781, NM_000037, AL713762, NM_139241, NM_001511, NM_021992, AK074050, NM_018424, NM_015000, NM_005893, NM_024430
21	anatomical structure development	3.42E-03	NM_003955, NM_004260, NM_000641, NM_001234, NM_004464, NM_174936, NM_000037, NM_032420, NM_001015053, NM_002765, NM_021067, NM_016931, NM_005602, NM_138711, NM_005938, NM_000059, NM_012242, NM_001017535, NM_015967, AK025855, NM_000095, NM_002133, NM_138375, NM_002402, NM_015894, NM_001262, NM_133330, NM_133336, NM_003920, NM_005985, NM_145804, NM_019885, NM_000057, NM_001147, NM_005587, NM_172164, NM_002359, NM_153487, NM_005225, NM_139314, NM_015895, NM_002448, CD619445, NM_005429, AK074711, NM_002061, NM_013370, NM_007177, NM_000266, NM_023004, NM_004737, NM_018371, NM_001846, NM_170589, NM_001964, NM_004734, NM_002562, NM_006080, AL713762, NM_139241, NM_001511, NM_000596, NM_006561, NM_002210, NM_007068, NM_007174, NM_004626, NM_001753, NM_170735, U68019, NM_005902, NM_005410, NM_153618, NM_013277, NM_002579, NM_001005463, NM_006096, NM_005893, NM_003900, NM_004881, NM_014288, NM_012291, NM_138639, NM_000465, NM_004118, NM_017613, NM_007295, NM_001012271, NM_004091, NM_013982, NM_001003395, NM_002315, NM_139211, NM_024323, NM_018063, NM_003483, NM_004629, NM_001316, NM_018204, NM_006733, NM_000332, NM_198098, NM_018945, NM_021012, NM_000723, NM_012072, NM_003835, NM_020169, NM_000185, CB243784, NM_006528, NM_003104, NM_001049, NM_006895, NM_004925, NM_013445, NM_144492, NM_004753, NM_000189
13	nucleotide binding	3.67E-03	NM_005914, NM_007068, NM_182802, NM_000057, NM_002915, NM_004526, NM_181471, NM_182776, NM_002875, NM_181578, NM_003786, NM_024857, NM_014109, AI085037, NM_182964, NM_000392, NM_022092, NM_005781, NM_006444, NM_005030, NM_174858, NM_004260, NM_015000, NM_032844, NM_003318, NM_018492, NM_080725, NM_020242, NM_001033, AK056691, NM_198433, NM_005496, AF339799, NM_182687, NM_014278, NM_031217, NM_004734, NM_003579, NM_006845, NM_004523, NM_007174, NM_003384, NM_018063, NM_199420, NM_015148, NM_004336, AK074050, NM_014791, NM_000189, NM_012393, NM_022116, NM_014264, NM_006187, NM_001009954, NM_006452, NM_002395, NM_002562, NM_025130, NM_016931, NM_015569, NM_194272, NM_153020, BC048985, NM_016937, NM_002691, NM_145654, NM_006561, NM_030941, NM_004753, NM_001789, NM_174936, NM_002661, NM_148170, NM_001814, NM_003686, NM_001015053, NM_024590, NM_018945, NM_004420, NM_005192, NM_015967, NM_182625, NM_012291, NM_002133, NM_015430, NM_014905, NM_004900, NM_001946, NM_004111, NM_152426, NM_020799, NM_006397, NM_015944, NM_014750, NM_153332
14	regulation of DNA replication	4.39E-03	NM_002266, NM_003504, NM_002592, NM_000057, NM_007295, NM_030928, NM_000059, NM_015895, NM_002875, NM_005938
16	DNA replication factor C complex	4.61E-03	NM_002592, NM_002915, NM_181471, NM_181578
20	structure-specific DNA binding	5.85E-03	NM_007295, NM_000059, NM_004111, NM_016937, NM_003579, NM_002875, NM_006479, NM_005914, BC048985, U68019, NM_005902, NM_182776
24	helix-hairpin-helix motif	9.66E-03	NM_003686, NM_182625, NM_004111, NM_153332, NM_002691, NM_006397, NM_030941, NM_016937
27	kinase activity	0.011	NM_001789, NM_001826, NM_182687, NM_001262, NM_057749, NM_016323, NM_005192, NM_001003395, NM_001234, NM_002895, NM_183404, NM_005613, NM_001753, NM_004420, NM_001946, NM_002061, NM_001012271, NM_000057, NM_174936, NM_002133, AL713762, NM_139241, U68019, NM_005902, NM_139314, NM_004629, NM_003955, NM_015000, NM_018098, NM_003900, AK056691
26	chromosome localization	0.014	NM_001012271, NM_014750, NM_080668, NM_012291
19	chromatin establishment/ maintenance	0.014	NM_003483, NM_006444, NM_004260, NM_000057, NM_004219, NR_002734, NM_172164, NM_001005414, NM_001809, NM_002895, NM_183404, NM_006607, NM_015341, NM_003609, NM_001015053, NM_012117, NM_022909, NM_000059, NM_006101, AK056691, NM_080668, NM_022346, NM_005496, NM_012291, NM_003516, NM_014750, NM_005483, NM_005441, NM_004526, NM_018063, NM_133330, NM_133336, NM_004091
22	negative regulation of transcription	0.017	NM_013982, NM_003920, NM_003955, NM_144665, NM_000057, NM_000641, NM_001234, NM_002895, NM_183404, NM_003597, NM_005225, NM_001015053, NM_001049, NM_005397, NM_016931, NM_007295, NM_138711, NM_005938, NM_000059, NM_139314, NM_012242, NM_005192, NM_015895, NM_001017535, NM_002448, NM_182908, AK074711, NM_002061, NM_001012271, NM_013370, NM_003504, NM_030928, NM_001964, NM_014583, NM_013432, NM_002133, NM_002562, NM_006080, NM_005613, NM_001511, NM_001753, NM_000465, NM_018063, NM_003834, U68019, NM_005902, NM_001262, NM_003835, NM_013282, NM_018664, NM_004219, NM_004091, NM_005587, NM_003472, NM_002359, NM_003900
28	cyclin	0.022	NM_001262, NM_057749, NM_005192, NM_004701, NM_002133, NM_138375, NM_031966, NM_002895, NM_183404, NM_004881, NM_144665, NM_001034
18	spindle organization & second messenger signaling	0.029	NM_004523, NM_003981, NM_001005414, NM_006461, NM_006101, NM_003318, NM_198433, NM_002592, NM_001071, NM_004111, NM_001049
25	GTPase/enzyme regulator activity	0.031	NM_005781, NM_003955, NM_014783, NM_001003395, NM_015632, NM_004219, NM_000185, NM_006528, NM_006716, NM_002915, NM_139314, NM_015310, NM_018948, NM_001012271, NM_013296, NM_002883, NM_138375, NM_133489, NM_005613, AL713762, NM_139241, NM_001511, NM_007174, NM_001826, NM_002592, NM_018098, NM_003834, NM_001262, NM_057749, NM_020169, NM_003835, NM_175623, NM_152329, NM_203467, NM_032818, NM_013277
29	brct	0.045	NM_018098, NM_007295, NM_000465

Table 13: Transcription factor regulation of conserved shear-responsive genes. CARRIE analysis of the set of 574 conserved shear-responsive probes identified transcriptional regulators predicted to be involved in shear stress-triggered signaling. P-values and fold-change data for the set of 574 conserved shear-responsive probes were analyzed using the CARRIE server for each cell type, MSCs and ECs. Transcription factors predicted to be significantly ($p < 0.05$) involved appeared for one cell type (MSCs: 49 TFs, lower left; ECs: 113 TFs, right) or both (26 TFs; top left).

Matrix Name	EC P-value	MSC P-value
Transcription Factors Significant in Both ECs and MSCs		
hepatic leukemia factor	2.06E-12	9.25E-03
CCAAT/enhancer binding protein alpha	1.11E-07	8.59E-04
Retroviral TATA box	1.40E-07	3.98E-02
hepatic nuclear factor 1	2.65E-07	8.10E-03
Cart-1 (cartilage homeoprotein 1)	3.50E-07	3.06E-06
Hepatic nuclear factor 1	3.60E-07	4.66E-02
myogenic enhancer factor 2	5.56E-06	3.90E-02
RSRFC4	5.61E-06	2.38E-03
E4BP4	2.00E-05	4.55E-03
myocyte enhancer factor	4.63E-05	1.77E-03
cellular and viral TATA box elements	4.86E-05	2.39E-02
C/EBP	5.59E-05	3.95E-02
NKX6-1	1.01E-04	1.26E-03
LIM homeobox transcription factor 3	1.08E-04	4.97E-03
glucocorticoid receptor	1.18E-04	8.75E-04
Max	2.62E-04	8.94E-04
aryl hydrocarbon / dioxin receptor	3.82E-04	2.03E-02
HNF-1	7.86E-04	4.65E-02
E2F-1	1.29E-03	1.18E-02
related to serum response factor, C4	1.43E-03	1.24E-03
E2F-1	2.17E-03	1.46E-02
NK related homeobox factor 6-2	3.38E-03	2.33E-02
activator protein 1	1.14E-02	1.17E-02
cell division control protein 5	1.40E-02	2.42E-02
c-Myc/Max heterodimer	2.14E-02	8.94E-04
androgen receptor	3.10E-02	4.33E-04

Matrix Name	EC P-value	MSC P-value
Transcription Factors Significant only in MSCs		
activator protein 2	--	9.96E-13
AP-2gamma	--	1.04E-12
AP-2	--	1.05E-11
NF-kappaB (p50)	--	2.18E-08
ETF	--	2.44E-07
AP-2alpha	--	6.03E-06
estrogen receptor	--	2.80E-04
NF-kappaB	--	4.36E-04
PEA3	--	6.66E-04
GA binding protein	--	8.68E-04
LBP-1	--	8.98E-04
Tax/CREB complex	--	1.26E-03
upstream stimulating factor	--	1.79E-03
activating transcription factor 3	--	2.42E-03
c-Ets-2 binding sites	--	2.42E-03
zinc finger with interaction domain	--	2.43E-03
zinc finger protein of the cerebellum 2	--	2.49E-03
LF-A1	--	2.50E-03
activator protein 4	--	3.37E-03
HSF	--	3.44E-03
PU.1	--	3.55E-03
EGR	--	4.57E-03
runt-factor AML-1	--	4.72E-03
tumor suppressor p53	--	6.26E-03
Pax	--	8.25E-03
ETS	--	9.16E-03
USF	--	9.16E-03
MAZ	--	9.35E-03
sterol regulatory element-binding protein 1	--	1.17E-02
PPAR-gamma (peroxisome proliferator-activated receptor gamma)	--	1.26E-02
c-ETS-1 binding site	--	1.42E-02
MAZ related factor	--	1.43E-02
SREBP	--	1.43E-02
MZF1	--	1.46E-02
aryl hydrocarbon / Arnt heterodimers, fixed core	--	1.61E-02
neuron-restrictive silencer factor	--	1.96E-02
aryl hydrocarbon receptor / Arnt heterodimers	--	2.30E-02
E47	--	2.39E-02
Tax/CREB complex	--	2.39E-02
hypoxia induced factor	--	2.40E-02
Sp3	--	2.40E-02
c-Myc/Max binding sites	--	2.44E-02
Yin and Yang 1	--	3.31E-02
LXR	--	3.32E-02
MTF-1	--	3.36E-02
signal transducer and activator of transcription 5a	--	3.44E-02
AML	--	3.91E-02
activator protein 1	--	4.75E-02
AML1	--	4.84E-02

Matrix Name	EC P-value	MSC P-value
Transcription Factors Significant only in ECs		
HFH-4	3.92E-18	--
modulator recognition factor 2	1.47E-16	--
AFP1	2.60E-16	--
HNF-3alpha	1.08E-11	--
sex-determining region Y gene product	6.70E-11	--
HNF-3	1.17E-10	--
fork head box J 2	1.36E-10	--
myocyte enhancer factor	2.44E-10	--
HFH-3 (HNF3/fork head homolog 3)	8.36E-10	--
transcriptional repressor CDP	9.18E-10	--
FOX	1.35E-09	--
fork head box J 2	1.94E-09	--
octamer factor 1	1.28E-08	--
SOX (SRY-related HMG box)	3.22E-08	--
Crx	3.32E-08	--
HNF-6	3.42E-08	--
NK class homeobox factor 3A	1.32E-07	--
Fork head RElated ACtivator-2	1.61E-07	--
myogenic MADS factor MEF-2	4.30E-07	--
TATA binding protein	4.64E-07	--
fork head box O1	4.81E-07	--
HOXA4	5.37E-07	--
CCAAT/enhancer binding factor	5.61E-07	--
POU factor Brn-2	6.27E-07	--
fetal Alz-50 clone 1	1.20E-06	--
Fork head RElated ACtivator-4	1.84E-06	--
C/EBPgamma	4.26E-06	--
myogenic MADS factor MEF-2	8.82E-06	--
POU3F2	1.26E-05	--
fork head box O3	1.30E-05	--
fork head box O4	1.30E-05	--
fork head box D3	1.41E-05	--
YY1	1.51E-05	--
Fork head RElated ACtivator-7	1.62E-05	--
CCAAT/enhancer binding protein beta	1.75E-05	--
fork head box O1	1.80E-05	--
octamer-binding factor 1	2.56E-05	--
homeo domain factor Pbx-1	2.58E-05	--
C/EBPdelta	5.59E-05	--
octamer factor 1	7.10E-05	--
Glucocorticoid response element	9.28E-05	--
sex-determining region Y gene product	1.10E-04	--
TEF	1.10E-04	--
Fork head RElated ACtivator-3	1.29E-04	--
CHX10	1.31E-04	--
octamer-binding factor 1	1.34E-04	--
GATA-binding factor 1	1.37E-04	--
IPF1	1.39E-04	--
Pbx-1	1.52E-04	--
Nuclear factor of activated T-cells	1.96E-04	--
E2F	2.48E-04	--
POU1F1	2.88E-04	--
E2F	2.97E-04	--
X-box binding protein RFX1	3.18E-04	--
E2F	3.63E-04	--
octamer factor 1	3.75E-04	--
Octamer binding site	4.81E-04	--
fork head box O4	5.14E-04	--
AP-3	7.20E-04	--
cut-like homeodomain protein	8.30E-04	--
E2F	9.57E-04	--
E2F	1.08E-03	--
E2F	1.28E-03	--
octamer factor 1	1.77E-03	--
ATF-1	1.96E-03	--
CRE-binding protein 1/c-Jun heterodimer	2.17E-03	--
NK2 class homeobox factor 2	2.67E-03	--
Rb/E2F-1/DP-1 trimeric complex	3.45E-03	--
myogenic MADS factor MEF-2	3.67E-03	--
MIBP-1 / RFX1 complex	3.96E-03	--
TCF11/KCR-F1/Nrf1 homodimers	4.18E-03	--
E2F-4/DP-1 heterodimer	4.22E-03	--
CCAAT/enhancer binding protein beta	5.40E-03	--
Meis-1a/HOXA9 heterodimeric binding	5.40E-03	--
MYB	5.70E-03	--
cAMP-responsive element binding protein 1	5.79E-03	--
AREB6 (Atp1a1 regulatory element binding factor 6)	5.83E-03	--
c-Myb	7.28E-03	--
PPAR (peroxisome proliferator-activated receptor gamma)	8.32E-03	--
NF-Y	8.81E-03	--
POU3F2	9.22E-03	--
heat shock factor 1	9.24E-03	--
paired box factor 2	9.39E-03	--
GATA	9.67E-03	--
IRF1	9.67E-03	--
Hand1/E47 heterodimer	1.06E-02	--
POU-factor Tst-1/Oct-6	1.06E-02	--
B-cell-specific activating protein	1.13E-02	--
GATA binding site	1.42E-02	--
X-box-binding protein 1	1.63E-02	--
serum response factor	1.69E-02	--
CCAAT/enhancer binding protein	1.72E-02	--
STAT	1.72E-02	--
GATA-binding factor 2	1.78E-02	--
SRF	1.99E-02	--
GATA-binding factor 1	2.09E-02	--
Meis-1b/HOXA9 heterodimeric binding	2.09E-02	--
cut-like homeodomain protein	2.20E-02	--
serum response factor	3.00E-02	--
AREB6 (Atp1a1 regulatory element binding factor 6)	3.16E-02	--
58 KDA repressor protein	3.21E-02	--
AP-1 binding site	3.31E-02	--
octamer factor 1	3.46E-02	--
TEF-1	3.50E-02	--
X-box binding protein RFX1	3.69E-02	--
nuclear factor Y (Y-box binding factor)	3.90E-02	--
pituitary homeobox factor 2	3.90E-02	--
GATA-6	3.94E-02	--
GATA-binding factor 3	3.99E-02	--
complex of Lmo2 bound to Tal-1, E2A proteins, and GATA-1, half-site 2	4.03E-02	--
CREB	4.23E-02	--
octamer factor 1	4.51E-02	--
cAMP-responsive element binding protein	4.63E-02	--

CHAPTER VII

DISCUSSION

The data presented here collectively describe MSCs vascular-relevant mechanosignaling, with direct comparisons to signaling responses observed in SMCs or ECs exposed to cyclic strain or shear stress, respectively. MSCs have muted responses to applied force, compared with differentiated vascular cells, in terms of the number, magnitude fold change, significance of difference, and/or rate of gene expression change (Chapters 3 and 5). Gene profiles assessed using whole genome microarrays demonstrate that sample groups assessed differ primarily in their overall expression profiles, and less so in terms of the applied force environment (Chapters 4 and 6). In all cases (Chapters 3-6), a limited set of genes differ significantly in response to applied force in multiple cell types (MSCs and SMCs or MSCs and ECs) and occasionally multiple types of applied force (cyclic strain and steady laminar shear stress). These instances of molecular responses to applied force that are significant and similarly altered in more than one cell type are defined as 'conserved' mechanoresponses. Conserved mechanoresponses related to immune and inflammatory function and oxidative stress are detected using qPCR following either cyclic strain (Chapter 3: Il8, Vcam1, Hmox1) or shear stress (Chapter 5: Cox2 and Hmox1). Genome analysis of conserved strain- or shear-responsive molecules indicates conserved force-responsive molecules can be found across multiple subcellular locations and affect a broad range of molecular functions, but are unevenly distributed throughout the genome. This suggests chromosomal location may be important for determining mechanosensitivity at the transcript level. Functional analysis of conserved force-responsive genes predicts that cell proliferation and regulation of oxidative stress are the most significant functions commonly regulated by these mechanical strains and stresses.

7.1 Limitations of Experimental Design

The objective of this dissertation was to contrast the signaling responses of MSCs and differentiated vascular cells in response to applied mechanical cues. Experiments were designed to provide paired data for each cell type and matched conditions between cell types. However, based on the specific experiments completed, the resulting collection of data focuses on changes in gene expression levels of specific types of mechanical cues (equibiaxial cyclic strain or steady laminar fluid shear stress) at a few instances of force magnitude, frequency and duration. Furthermore, the mechanoresponse of each cell type was assessed using few donors: one donor each for SMCs and ECs, and two donors for MSCs. These inherent experimental parameters (cell source, force condition, and gene-based signaling assessment) limit the breadth of conclusions that can be drawn from this work.

Gene expression is one means by which to assess changes in cell signaling. Cell signaling changes also occur at the chromosomal, protein, and post-translational levels. Changes in gene expression level are suggestive, but not definitive, of subsequent signaling changes. Thus, determining the functional significance of the gene expression changes observed throughout these studies requires additional studies assessing multiple regulatory stages. Inclusion of functional assessments when possible (e.g., leukocyte binding) would strengthen conclusions regarding the impact of non-vascular-like mechanosignaling of MSCs. Thus, conclusions made about cellular mechanosensitivity based on studies included in this dissertation are limited to the gene expression level, with the exception of protein quantification of VE-Cad, Pecam1, and vWF completed as part of shear stress studies. Statements made about the functional impact of gene expression changes are suggestive, not definitive.

In terms of mechanosignaling, work by others and presented here shows that cell signaling responses to mechanical cues is a dynamic process. Force parameters including duration, magnitude, frequency, 2-D versus 3-D presentation, and surface chemistry can

influence cellular response to mechanical force. This limitation in terms of the range of mechanical parameters tested is typical of published mechanosignaling to date. Studies from this dissertation compare disparate entities (e.g., stem cells versus differentiated cells; cyclic strain versus shear stress) in an attempt to identify patterns of mechanosensitivity and overcome the limitations of few applied force conditions. However, this pragmatic limitation would be optimally addressed by finding a generalized understanding of how cell's interpret mechanical cues.

Use of primary cells introduces another variable: donor history. Properties of MSCs can vary with donor. Work by others has shown that proliferation rate of MSCs and differentiation potential decrease with donor age. Efficiency of differentiation along different lineages can vary with donor. Harvest of MSCs can be reduced in diseased patients. Until we have more definitive markers to identify MSCs, comparing results across MSCs derived from multiple donors is necessary to separate properties of MSCs from biological noise related to age, gender, ethnicity, genotype, or disease state of the donor. Differences in signaling are likely to vary more between different cell types (as supported by microarray two-factor ANOVA) than between different donors of the same cell type. For this dissertation, signaling differences were compared across different cell types derived from different donors. Defining conserved force-responses based on data from different cell types is theoretically a more stringent criterion than different donors within a single cell type. It is still possible that some molecules, while exhibiting a conserved mechanoresponse in multiple cell types, vary from person to person in their basal expression levels of these molecules. Repeating studies included in this dissertation with cells derived from different donors could confirm the conserved nature of the mechanoresponses observed and clarify donor-to-donor variability.

Another challenge related to heterogeneity of MSCs, independent of individual donor charateristics, is the phenotypic variation in isolated MSCs. The lack of unique selection markers for MSCs and highly heterogeneous cell population within the bone marrow permit a broader range of cells to be isolated even with standard isolation procedures. Mesenchymal stem cell-like cells have been isolated using a range of methods, including

gradient separation and mononuclear cell plating and immunoselection, and have been isolated from a range of tissues. Lack of standard source, isolation, and definition make forming generalizable conclusions about MSCs difficult [302]. Finally, in vitro culture may trigger additional phenotypic changes in MSCs compared to their in vivo responses. For these studies, the variability within MSCs populations is predicted to be similar or less than the variability in cell signaling between MSCs and differentiated vascular cells. Comparing inherently heterogeneous populations of MSCs with differentiated vascular cells is thus a more stringent method of identifying force-repsonsive molecules conserved across cell type. Since molecular assessments were completed at the population level, heterogeneity in MSCs implies that force-responses specific to MSCs could be either a property of the entire population or of a subset of cells.

These limitations trigger follow-up questions to more explicitly test trends observed in these studies. Multiple follow up studies will be required to determine the significance and broad applicability of the numerous specific gene expression changes detected in this dissertation. The limitations of this work mean that this assessment of mechanoresponse is not comprehensive. Based on the study design though, comparing signaling data across multiple experiments for multiple cell types, conclusions about conserved mechanoresponse genes are anticipated to include more false negatives (incomplete 'mechanome') than false positives.

7.2 Responses to Cyclic Strain

Cyclic strain mechanosignaling comparisons of MSCs and SMCs identify specific molecules whose expression varies with applied cyclic strain. These cell types differ in terms of basal gene expression and strain-responsive transcriptome changes. A subset of molecules are conserved strain-responsive in MSCs and SMCs. Signaling responses of MSCs and SMCs to cyclic strain were compared in terms of signal transduction genes (PCR arrays, Chapter 3) and strain-responsive transcriptomes (microarrays, Chapter 4). Data from Chapters 3 and 4 corroborates the marked differences in basal gene expression profiles of MSCs and SMCs (Figures 7 and 16). Accuracy of microarray results could be confirmed using

qPCR results (Chapter 3) for strain-responsive genes in SMCs (Cebpb, Il1α, Il8, Hmox1, Rbp1, and Tfrc). For SMCs, discrepancies in microarray versus standard qPCR strain-responsive genes could often be eliminated by including molecules from the same protein family (N-Cam and Pecam1 vs. Vcam1; Irf-2,-3,-7, and -9 vs. Irf1; Mmp19 vs. Mmp7). Some discrepancies in data indicate gene expression assessment does not have 100% fidelity across detection method. For example, Il1α strain-responsiveness was significant by both PCR array and microarray, but could not be verified with subsequent qPCR. Strain-responsive genes in MSCs verified with PCR arrays and microarrays included Vcam1, Bmp4, Selplg, and members of the Hox (Hox-A9, -B3, -B4, -B6, -C6, -C10, -D3, and -D9 and vs. Hox-A1) and Interleukin (related to Il-1, -3, -6, -7, -10, -13, -15, -17, -20, -21, and -22 versus Il8) families. Magnitude expression changes were greater in SMCs than MSCs (Figures 1 and 17). Conservation of fold-change response, rather than absolute expression level, has been proposed as a regulatory mechanism in other systems [82, 83]; data presented in Chapter 3 indicates this mechanism applies to mechanosignaling as well (Figure 9).

Results from Chapter 3 suggested more genes in SMCs than MSCs may alter expression levels in response to applied strain, based on larger numbers of genes identified using graded p-value thresholds (Figure 9). However, similar analysis performed on microarray results contradicts this conclusion, suggesting instead that MSCs and SMCs have similar total numbers of significantly strain-responsive genes ($p < 0.001$: 176 vs. 109; with $|FC| > 1.5$ applied, 36 vs. 39). This difference could be due to the larger sample pool in microarrays compared to PCR arrays: $\tilde{4}$4,000 probes versus 84 genes. In this case, both cell types appear similarly mechanosensitive in terms of the number of genes with expression significantly ($p < 0.05$) altered by force. An alternate explanation is that signal transduction genes specifically are more sensitive to cyclic strain in SMCs than MSCs.

7.3 Responses to Shear Stress

Signaling responses to fluid shear stress were compared between MSCs and ECs using a panel of immune and inflammatory markers (Chapter 5) and whole genome microarrays

(Chapter 6). MSCs rearranged to form gaps between cells in response to shear stress on Type I Collagen-coated layers (Figure 22). To ensure a homogenous cell monolayer, and therefore more uniform application of shear stress in microarray experiments, MSCs were exposed to shear stress on fibronectin-coated surfaces since fewer gaps between cells appeared following applied shear stress (Figures 28 and 31). No marked difference in alignment to shear stress was observed in ECs on fibronectin versus type I collagen surfaces, suggesting the change in protein adhesive surface does not affect the rate of endothelial cell rearrangement.

In spite of a difference in underlying protein substrate, signaling changes detected in samples exposed to shear stress were reproduced on both fibronectin- and type I collagen-coated surfaces. In ECs, shear-responsive genes identified in microarrays and qPCR included Pecam1, vWF, Cox2, eNos, Hmox1, Klf2, and Mcp1 (Ccl2), and members of the Cadherin family (Cdh-3, -4, -10, -11, -13, -19 and several protocadherins versus VE-Cad). In MSCs, Hmox1, Mcp1, and Klf2 family members (Klf-9, -11, and -15 versus Klf2) altered gene expression in response to applied shear stress. Lack of Pecam1 shear-response detected by microarrays is consistent the biphasic shear-response of Pecam1 detected with qPCR. On type I collagen surfaces, Pecam1 expression significantly increased following 12 hours of applied shear stress, but significantly decreased following 48 hours of applied shear (Figure 24). Genes whose expression did not significantly alter in qPCR assessments, including VE-Cad, Cox2, and eNos, also were not significantly altered in microarray assessment. Matched shear-responses in Chapters 5 and 6 corroborate the conclusion made in Chapter 5, that lower expression of Pecam1 and VE-Cad in MSCs than ECs exposed to shear stress may result in reduced immune activation.

Single factor studies included in Chapter 5 highlighted the force magnitude-dependence of some shear stress gene responses (ECs: eNos, Klf2, vWF; MSCs: Mcp1; Both: Cox2). Immunocytochemistry studies also contrasted gene and protein shear stress responses, suggesting Pecam1 and VE-Cad gene changes also affect downstream protein levels. In contrast to these single factor studies, microarray comparison of shear-responsive transcriptomes suggests shear stress affects signaling in ECs more than MSCs in terms of

number, magnitude fold-change, and significance of gene expression changes (Figures 33 and 34). High-throughput signaling data generated with microarrays enabled identification of potential convergence nodes controlling shear stress responses and uncovered strong correlation between conserved shear-responsive molecules and cell cyclic and DNA replication control. Shear stress regulation of cell cycle correlates with previous reports of endothelial cell shear responses and with the decrease in cell number observed in MSCs (Figure 23).

7.4 Comparison of Cyclic Strain and Shear Stress Mechanosensitive Gene Expression

Four mechanosensitive transcriptomes were generated as part of these studies, representing three cell types (MSCs, SMCs, ECs) and two force types (cyclic strain, shear stress). PCA analysis was able to separate samples based on cell type for both cyclic strain and shear stress. PCA analysis separated samples based on force condition (static versus applied force) more so in shear stress comparisons, for both MSCs and ECs, than strain comparisons, although SMCs static and strain samples separated more than MSCs static and strain samples. MSCs and SMCs strain responses appeared to vary in opposite directions in terms of principal component 3. More samples, preferably incorporating additional cell donors, would verify this preliminary data.

For high-stringency force-responsive criteria ($p < 0.001$, n=3; $|FC| \geq 1.5$), strain responses identified genes in MSCs (36) and ECs (39), compared to shear responses in which MSCs (55) and ECs (462) genes were identified. A greater number of significant gene expression changes were observed following shear stress than cyclic strain at both lower stringency force responsive criteria ($p < 0.05$) and when considering only MSCs. Unlike SMCs or ECs, MSCs are not preconditioned to these particular mechanical cues. This indicates the pattern of more genes significantly affected by shear stress than cyclic strain could apply beyond differentiated vascular cells. The biological importance of specific gene mechanosignals, or of many or few gene expression changes, remains unknown.

Two sets of conserved force-responsive genes were defined: conserved strain-responsive

molecules (442 microarray probes with $p < 0.05$ for MSCs, SMCs, and two-factor ANOVA force-dependence) and conserved shear-responsive molecules (574 microarray probes for $p < 0.05$, $|FC| > 1.5$ for MSCs, ECs, and two-factor ANOVA force-dependence). Comparing set lists of conserved strain-responsive molecules with conserved shear-responsive molecules reveals that approximately 7% of these molecules (34 probes) have expression sensitive to both force types in all three cell types. Although only a few genes were mechanosensitive compared to the total number assessed, recurring gene expression changes following applied mechanical force may indicate these molecules are biologically important regulators of cell physiology.

To highlight patterns in mechanosignaling, conserved gene lists for shear stress and cyclic strain were abstracted in terms of predicted transcriptional regulatory pathways, chromosomal distribution, signaling networks, and GO terms (biological processes, molecular functions, and cellular locations). More transcription regulators were predicted to be significantly involved in shear response than strain response, although some factors were predicted to regulate responses to both forces (e.g., myogenic enhancing factor 2). Distribution of conserved force-responsive genes throughout the chromosomes was not uniform. In shear stress comparisons, but not strain, a signaling network directly connecting many conserved shear responsive molecules was identified. This network highlighted multiple hourglass motifs, suggesting shear-responses may be funneled through a limited set of regulatory molecules.

To eliminate effects due to variation in chromosome length, the number of force-responsive molecules was normalized to either DNA length, number of genes, or protein coding length. In both strain and shear stress, chromosomes 4 and 11 had unusually high force-responsive genes per total number of genes (ratios above 95% confidence interval for both chromosomes and both force types) and per coding length (ratios above 97% for chromosome 11 in both shear and strain; above 95% or 68% for chromosome 4 response to shear or strain). This inhomogeneity suggests the increase in force-responsive genes present on chromosomes 4 and 11 does not occur by chance. Increased force-sensitivity of a chromosome could be due to a particular nuclear architecture, chromosome structure, or

a sequence of DNA that is more sensitive to applied physical forces.

Approximately 50% of genes with force-responsive expression localized to the nucleus and cytoplasm, suggesting these locations are enriched for mechanoregulation at the gene level. Enzymes, transcription regulators, and multi-protein complex molecules were the primary molecular functions represented in both conserved strain and shear stress gene sets. Regulating transcription regulatory molecules through gene expression itself is a potentially efficient signaling control since transcript machinery is already engaged. These studies suggest enzymes may also be regulated by mechanical force through a transcriptional mechanism.

Biological functions associated with strain versus shear stress differ. Cyclic strain altering gene expression associated with oxidative stress signaling, ion homeostasis, and growth and metabolism regulation. Shear stress signals were strongly associated with cell cycle, DNA replication, spindles and chromosomes. Differences in functions regulated by applied force could be characteristic of the applied force type or could be related to regulation of different physiologic processes depending on anatomical function and location. Molecules defined as conserved strain-responsive or conserved shear stress-responsive, but not both, provide a mechanism by which cells can distinguish between different types of mechanical force. Conversely, the fact that a subset of conserved mechanoresponsive molecules respond to both cyclic strain and shear stress, in spite of different functional outcomes regulated by these mechanical forces, suggests these molecules may act as conduits for a mechanical signal instead of determinants of a functional output.

7.5 Mechanoresponse Varies with Underlying Protein Substrate

Cyclic strain or fluid shear stress were applied to MSCs seeded on a variety of underlying protein substrates. For cyclic strain, this list included gelatin, type I collagen, type IV collagen, and fibronectin. Shear stress studies of MSCs signaling occurred on type I collagen, type IV collagen, or fibronectin. MSCs appeared to remodel when seeded on type I collagen-coated surfaces and subjected to either strain [67] or shear stress (Figure 22).

These rearrangement effects were abolished or reduced when MSCs were exposed to mechanical cues seeded on type IV collagen-coated or fibronectin layers. These studies show that underlying protein substrate can affect the morphological response of cells to mechanical cues. Analysis completed as part of Specific Aim 1 (Chapter 3) also demonstrate that changes in underlying protein substrate can alter the signaling profiles within both MSCs and SMCs. This signaling study demonstrates that significant differences in expression of specific genes between MSCs and SMCs change, depending on the underlying protein (Table 4).

Work completed by others has shown that adhesion to particular extracellular matrix molecules such as fibronectin can alter cell signaling. Others have shown that changes in substrate stiffness affect cell signaling, in particular altering differentiation of mesenchymal stem cells and embryonic stem cells [71, 69, 180]. Thus, the changes in cell signaling and mechanoresponses observed here due to underlying protein substrate could result from chemical signaling changes or from differences in adhesive strength and elasticity. Age, body mass index, and differentiation state can also affect cell signaling response to mechanical force [85]. While the first two factors were not directly assessed in this work, the overall increase in mechanosensitivity of differentiated vascular cells compared to MSCs observed here supports a role for differentiation in determining mechanosensitivity.

7.6 Cellular Mechanisms to Sense Physical Forces

Several mechanisms have been proposed by which cells may convert environmental physical cues, including static and dynamics forces, into biochemical signals capable of impacting cell function. Quantitative computational and mathematical models have been developed to describe specific properties such as cell shape or growth [253, 173]. Conceptual models also exist, such as the tensegrity theory that relates cell behavior to the balance of hydrostatic and tensile forces acting on the cell [111]. Many recent studies have focused on the role of substrate stiffness in determining cell function [70], ranging from stem cell [69] to tumor [310] biology. Vogel recently provided a linguistic model for mechanobiology, in which components of the mechano-chemical signaling cascades are

classified as sensors, transducers, or responders [296]. The studies presented here focus on signaling effects of mechanical cues, rather than physics-based descriptions of molecular changes. High-throughput studies were intended to highlight potential network organization and/or key regulators of mechanosignaling, but a greater number of similar studies are needed before a model of high-throughput mechanosignaling can be developed and tested. Furthermore, this work address a gap in mechanobiology research to date: comparison of mechanosensing across disparate conditions (species, cell type, natural environment, etc.).

These studies focused primarily on changes in gene expression level. Since gene expression is typically downstream of a signaling regulatory network, the genes identified as force-responsive in this work may not necessarily directly sense force, but may be downstream of a signaling cascade containing force-detecting elements. Molecular categories with reported direct force-sensitivty include: stretch-sensitive ion channels [186]; G-protein coupled receptors and other membrane-bound proteins [172, 34]; the actin and intermediate filaments cytoskeleton [307]; cell-cell and cell-matrix adhesion molecules such as integrins and focal adhesions [17, 46]; and the nuclear membrane and DNA [284]. In many cases, a mechanical cue triggers a conformational change in the molecule and thereby alters the signaling state [174]. Mechanosensors in the vascular system have been studied in single-factor studies for several decades. Stretch-activated ion channels regulate vascular physiology [270, 75]. A trio of shear-responsive molecules including PECAM, VEGF, and VE-CAD interact with one another and directly sense applied shear stress in endothelial cells [290]. These molecules in turn can regulate G-protein coupled receptors, the initiator of many intracellular signaling cascades [324]. In addition, the glycocalyx has been proposed as a regulator of mechanosensing in endothelial cells [281]. While mechanical forces are known to affect smooth muscle cell functions including proliferation, differentiation, and extracellular matrix expression [116], less is known about the direct mechanosensors controlling these physiologic responses. Recent work has shown Rho GTPases to be involved of mechanosensing of both vascular cells and MSCs [20, 220]. For the conserved

gene expression targets of cyclic strain or shear stress identified in these studies, the direct mechanosensors are rarely known. In instances of both gene and protein expression changes (e.g., PECAM or VE-CAD in endothelial cells), mechanosensing may be autoregulated, sensing and affecting the same molecule. For other molecules, bioinformatics tools such as GeneSpring and IPA connected conserved force-responsive genes via indirect connections and relationships beyond the gene expression level. These associations may be suitable targets for follow up studies to identify the actual mechanosensing molecules. Finally, incorporation of new techniques, such as protein-coated magnetic bead manipulation, provides a new way to distinguish between mechanoresponsive and mechanosensing molecules [1].

7.7 Future directions

Results from this work could be used to motivate a range of future experiments. Proteomic studies matched to the microarray data conditions would enable correlation of gene expression changes with protein or post-translational modification. More specific follow up studies related to results from each chapter are listed below.

Cyclic Strain Response. Evaluate the functional importance of novel strain-responsive genes in SMCs. Determine if gene expression changes in Il8, Hmox1, and Vcam1 correlate with protein expression and activity. Determine whether altered levels of Il8 or Hmox1 gene or protein expression alters Vcam1 gene expression, confirming the regulatory triad predicted by Chapter 3. Determine whether signaling regulation occurs via direct contact or through other signaling intermediates.

Shear Stress Response. Correlate gene expression changes of panel of 8 immune and inflammatory markers to protein expression and activation. Compare functional differences of MSCs and ECs exposed to shear stress, in order to verify if MSCs have a reduced inflammatory environment and lower immune activation than ECs. Alter shear stress profiles, adding oscillatory and/or turbulent flow, to determine whether known variations in ECs shear-response are present in MSCs. Determine whether

differences in protein spatial localization between cell types relate to functional differences of Pecam1, VE-Cad, and vWF.

High-throughput mechanoresponse. Verify force-responsiveness of conserved, significantly force-responsive genes identified using microarrays. Repeat high-throughput studies using alternative assessments to mRNA, such as miRNA, protein expression, post-translational modifications, and metabolites; match resulting multi-level signaling data to determine whether trends seen at gene expression level are consistent. Assess Nrf2 oxidative stress signaling pathway to determine activity in MSCs and SMCs and alterations in reponse to applied cyclic strain. Quantify proliferation rates in MSCs and ECs exposed to shear stress, compared to static culture. Determine whether applied shear stress regulates cell cycle and DNA replication in other cell types.

The breadth of mechanoresponse data, ranging cell type to extracellular matrix substrate to high-throughput gene assessment, could be used to motivate other studies on molecules or functions of interest. Addition of more high-throughput, comparative mechanobiology studies to the literature will provide a foundation from which to build a generalized description of cell mechanosensing.

CHAPTER VIII

CONCLUSIONS

Mesenchymal stem cells are a promising therapeutic tool for a wide range of applications. In the clinic, they have already been used as part of bone marrow transplants and immune acceptance strategies (to avoid transplant graft-vs.-host rejection). Recent clinical trials are investigating MSCs use to treat a range of disorders: Graft versus Host Disease (GvHD), liver disease, diabetic foot ulcers, bone marrow transplantation, and myocardial infarcion (MI) [300, 80]. Cardiovascular disease remains a major burden on the healthcare system in terms of morbidity, patients affected, and cost of treatment. Biological repair mechanisms enabled by cell-based therapies are proposed to more effectively address multifactorial problems such as vessel occlusion, impaired vasoactivity, infarcted muscle, and promote angiogenesis. Previous studies have shown that MSCs may contribute to these effects via both paracrine and differentiation mechanisms. In addition, the potential of MSCs for autologous or allogeneic therapy; relative ease of cell harvest; prior FDA approval; and fewer ethical hurdles compared to embryonic-derived cell types are practical benefits of MSCs-based therapies.

This dissertation was designed to fill a gap in the knowledge about MSCs suitability for cardiovascular therapies: specifically, to determine whether MSCs respond to vascular-relevant applied physical forces similarly or differently from differentiated vascular cells. Signaling responses to equibiaxial cyclic strain were compared between MSCs and SMCs (Chapters 3 & 4). Responses to steady laminar fluid shear stress were compared between MSCs and ECs (Chapters 5 & 6). A combination of single factor assessment and multiple force conditions (Chapters 3 & 5) and single force condition with high-throughput assessments (Chapters 4 & 6) were employed to study vascular-relevant mechanosignaling. The original hypothesis, that signaling responses would be conserved between MSCs and differentiated vascular cells, was true for a minority of total force-responsive genes for both

cyclic strain and shear stress studies. This work highlights specific similarities and differences between MSCs and differentiated vascular cell response to applied mechanical forces.

8.1 MSCs Cyclic Strain Response Compared to SMCs

For this study, MSCs and SMCs were compared on fibronectin-coated silicione in response to equibiaxial strain (10%, 1 Hz) for up to 24 hours. Assessment of signaling transduction genes demonstrated that MSCs respond to strain with fewer number, magnitude, and speed of altered gene expression levels. The similarity of Il8, Vcam1, and Hmox1 strain-responses in both cell types, subsequently referred to as a 'conserved' mechanoresponse, indicated immune and inflammatory-related functions may be regulated by similar force-responsive mechanisms in both cell types. Microarray comparison of MSCs and SMCs strain-responses after 24 hours applied force confirmed the marked differences in signaling profiles observed between cell types and the limited number of strain-responsive genes relative to the total number of assessed genes ($< 10\%$). Functional analysis using bioinformatics software highlighted the Nrf2 oxidative stress response as the most significantly involved strain-responsive signaling pathway in each cell type. These cyclic strain studies indicates MSCs may mimic beneficial SMCs mechanoresponses related to immune, inflammation, and stress responses. Areas in which MSCs and SMCs mechanoresponses differ suggest that MSCs may adhere to sites of injury more than SMCs (based on increased P-selectin expression) and highlight new genes whose function and importance in SMCs biology is unknown.

8.2 MSCs Shear Stress Response Compared to ECs

MSCs and ECs were compared on either type I collagen- or fibronectin-coated glass in response to applied steady laminar fluid shear stress (5 or 15 dyn/cm^2) for up to 48 hours. Gene expression levels were markedly different between the two cell types under basal and shear stress conditions. On type I collagen-coated surfaces, MSCs and ECs response to shear stress differed in terms of cell alignment, gene and protein expression changes

in response to applied shear stress, and kinetics of expression change. Signaling differences for a panel of genes assessed at multiple shear stress magnitudes and durations indicates MSCs promote a reduced inflammatory or immunogenic environment compared to ECs. The significance of morphologic differences (e.g., cobblestone- versus spindle-shaped cells; appearance of gaps in response to shear stress) necessitates more work before MSCs can be used as a lumenal layer. Microarray comparison of MSCs and ECs shear response were completed on fibronectin-coated surfaces, since MSCs cellular rearrangements of MSCs were reduced compared to collagen type I surfaces. MSCs and ECs differed in terms of number, magnitude, and significance level of shear-sensitive gene expression changes. Samples could be clustered in separate cell type and shear stress specific groups, even more distinct than in the case of cyclic strain. Through multiple analysis methods, proliferation-related functions were identified as the most significant conserved shear stress response. This data indicate MSCs do not differentiate towards ECs within 48 hours applied shear stress, nor do they recapitulate many of the characteristic endothelial gene expression responses to shear stress. However, a reduced inflammatory environment may still mean MSCs can benefit vascular therapies.

8.3 Vascular-relevant Mechanobiology

These studies demonstrate that cells can respond to applied mechanical cues with changes in cell signaling, in spite of apparently unchanged visible morphology. When high-throughput (microarray) or semi-high-throughput (PCR array) approaches were used, a minority of genes were force sensitive ($\tilde{1}$0%). This is not because few genes were expressed, since a much larger fraction of the total set ($\tilde{5}$0%) significantly varied between cell types (MSCs vs. SMCs or MSCs vs. ECs). Of the force-sensitive genes, a fraction ($\tilde{2}$0%) were force-responsive in both cell types. We referred to these molecules as having 'conserved' mechanosensitivity, since this is a parsimonious explanation for the appearance of force-responsiveness in disparate cell types. The concept of mechanosensitivity as a function critical to normal cell physiology, and therefore under evolutionary selection pressure, has not been thoroughly investigated. Such evolutionary selection pressure, if it exists, may

'conserve' mechanoresponses based on sequence and domain homology, cell and tissue type (as shown here), or species type.

For both cyclic strain and shear stress comparisons, MSCs were observed to have reduced gene mechanosensitivity than differentiated vascular cells. Future studies could determine whether this is a function of differentiation state or merely these particular cell type comparisons (as would be suggested if MSCs and osteocytes or chondrocytes shared more similar mechanoresponse profiles). Finally, this work demonstrates that mechanoresponses can be conserved in terms of fold change, rather than absolute level of expression; do not rely solely on initial expression levels to determine output response; and suggests both median and variance may be used to track force-responsive genes. These studies used cell type-specific culture media. This approach was intended to reduce the effect of biochemical cues altering cell signaling, meaning that observed signaling changes were theoretically due only to the applied force condition. However, this means that cell type-specific mechanorespones, if dependent on initial biochemical conditions (e.g., a particular receptor in the media), could result from differences in cell culture media. Future studies are necessary before these examples of conserved mechanosensitivity can be generalized to broader mechanical or biological conditions.

8.4 Closing Remarks

This work has generated data contributing to vascular mechanobiology, biology and therapeutic potential of MSCs, and potential for a 'conserved' subset of mechanoresponses. Future studies to verify results from this work could address specific limitations of these studies: (1) incorporation of more cell type donors to confirm reproducibility of mechanoresonses within a specific cell type, (2) incorporation of additional cell types or species types to determine the extent of mechanosignaling conservation, and (3) assessment of cell signaling parameters other than gene expression levels (e.g., protein expression; protein activity; relative component levels). Studies focusing on one or a few mechanoresponsive molecules identified here are necessary to confirm the mechanism of force-sensitivity, associated signaling cascade, and ultimate functional impact. Finally, the focus of this particular work has

been to highlight mechanoresponses that are *similar* across disparate cell or force types. The experimental data set generated for this dissertation though could also be mined to examine cell type-specific mechanoresponses. Future studies could determine whether cell type-specific mechanoresponses are part of the essential traits that distinguish different cell types from one another.

This work indicates mesenchymal stem cells may be beneficial for specific aspects of a vascular therapy, such as modulating the immune or inflammatory response. These studies are among the first to describe MSCs sensitivity to vascular-relevant mechanical forces. Marked differences in signaling observed in these studies indicates MSCs are unlikely to adopt all vascular-like signaling patterns upon implantation. Systematic study of mechanoresponses, and prioritization of the benefits and risks of specific signaling responses, will help refine how MSCs can best contribute to vascular cell-based therapies.

APPENDIX A

CHARACTERIZATION OF MESENCHYMAL STEM CELLS

Human adult bone marrow-derived mesenchymal stem cells were purchased from Lonza (Catalog No. PT-2501). One lot of MSCs was used for experiments per force type. Lonza MSCs are characterized prior to sale for adipogenic (Oil Red O assay), chondrogenic (Proteoglycans-Safranin stain and Type II Collagen on Day 14 or 21), and osteogenic (Calcium deposition) differentiation. Cells are also tested for positive expression of CD105, CD166, CD29, and CD44 and negative for expression of CD14, CD34, and CD45.

The following information summarizes donor characteristics of lots used for these studies. Results from biochemical differentiation studies and flow cytometry are based on cells at experimental use passage (≤ 7 passages post-thaw).

A.1 Donor 1. Cyclic Strain Experiments

A.1.1 Background information

One lot of MSCs, representing cells harvested from a single donor, was expanded and used for cyclic strain experiments.

Donor traits

Lonza Product Code: PT-2501

Lot Number: 4F0591

Gender: Male

Ethnicity: Caucasian

Age: 32

Passage on thaw: P.2

A.1.2 Flow cytometry characterization

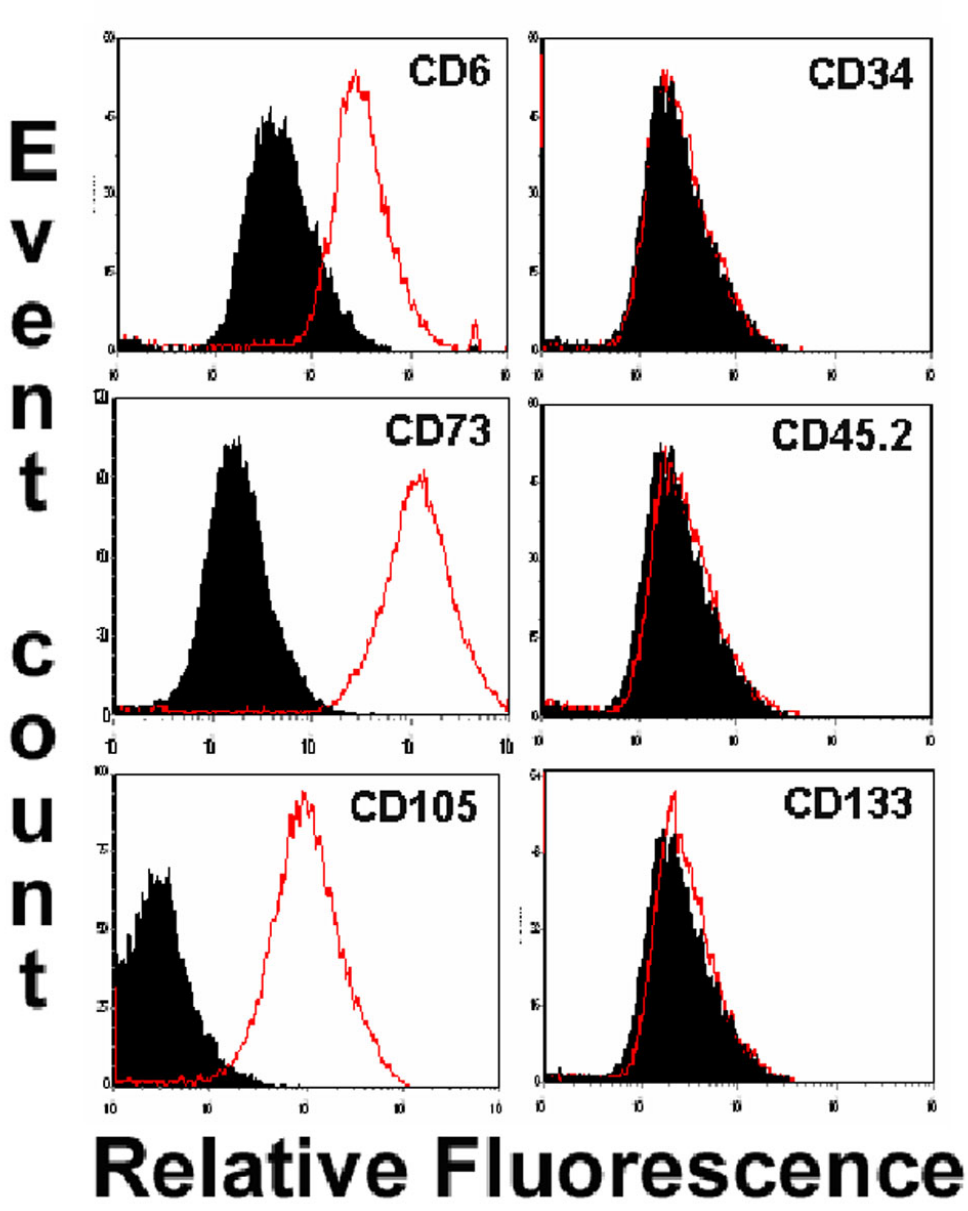


Figure 39: Flow cytometry characterization of Lot . Surface protein expression was assessed at experimental use passage P.6 for three positive markers, CD73, CD105, and CD166, and three negative markers, CD34, CD45, and CD133. Negative markers distinguish MSCs from other marrow-derived and hematopoeitic cell types. CD166 expression was determined using binding to its ligand CD6. Red = stained sample. Black = secondary or cells only control.

A.1.3 Biochemical Differentiation Results

A.1.3.1 Osteogenic

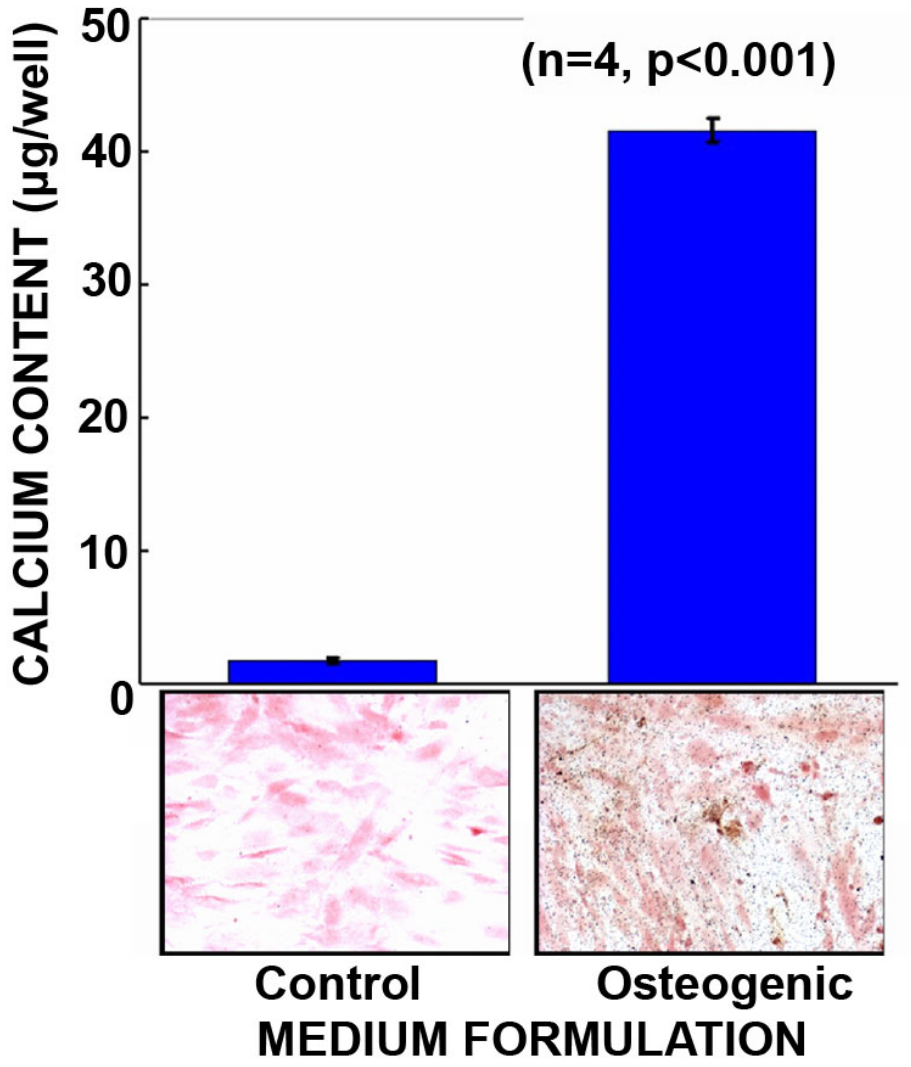


Figure 40: Osteogenic differentiation of Lot . MSCs were cultured in either osteogenic or standard MSC growth media. Deposition of calcium, an indicator of osteogenic differentiation, was assessed qualitatively with von Kossa staining and quantitatively using a Calcium (CPC) LiquiColor test (Stanbio). Nuclei were counterstained with nuclear fast red. Significance was determined using a two-tailed t-test.

A.1.3.2 Adipogenic

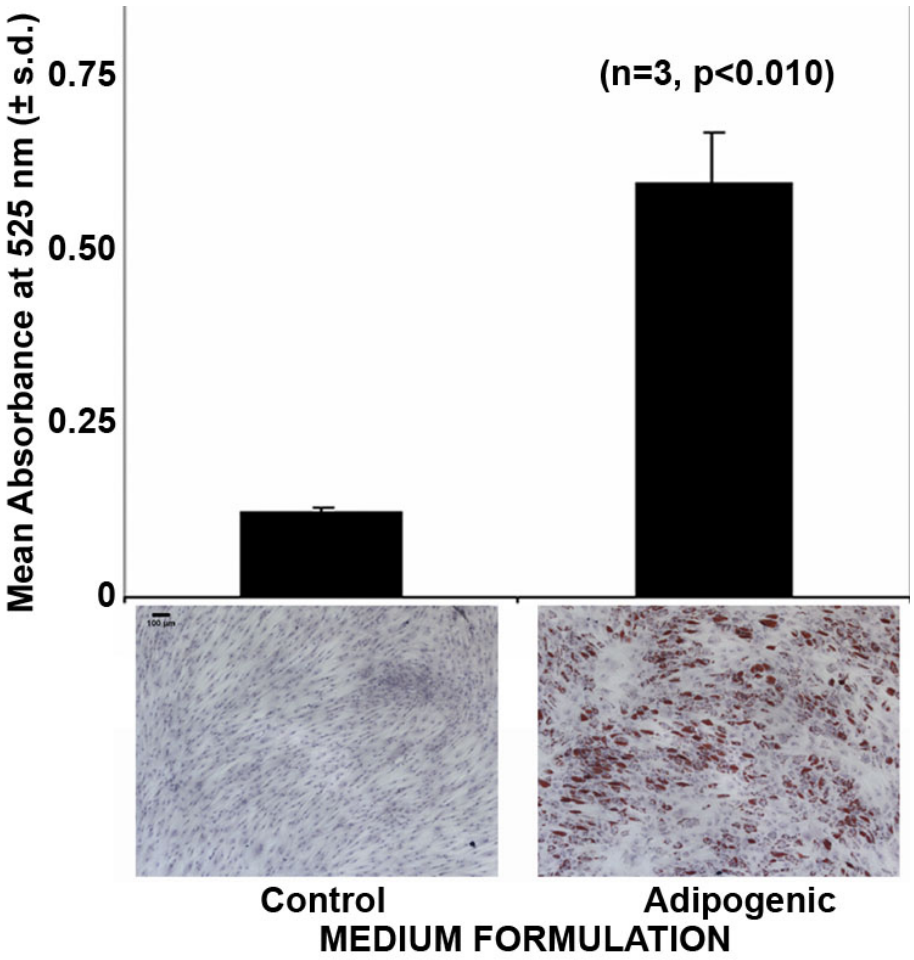


Figure 41: Adipogenic differentiation of Lot . MSCs were cultured in adipogenic or standard MSC growth media. Adipogenic culture media alternated between induction and maintenance media. Adipogenic differentiation was inferred from accumulation of lipid droplets, qualitatively and quantitatively assessed using Oil Red O staining and dye re-suspension, respectively. Nuclei were counterstained with hematoxylin. Significance was determined using a two-tailed t-test. Scale bars = 100μm.

A.2 Donor 2. Shear Stress Experiments

A.2.1 Background information

One lot of MSCs, representing cells harvested from a single donor, was expanded and used for shear stress experiments.

Donor traits

Lonza Product Code: PT-2501

Lot Number: 6F3837

Gender: Female

Ethnicity: Caucasian

Age: 34

Passage on thaw: P.2

A.2.2 Flow cytometry characterization

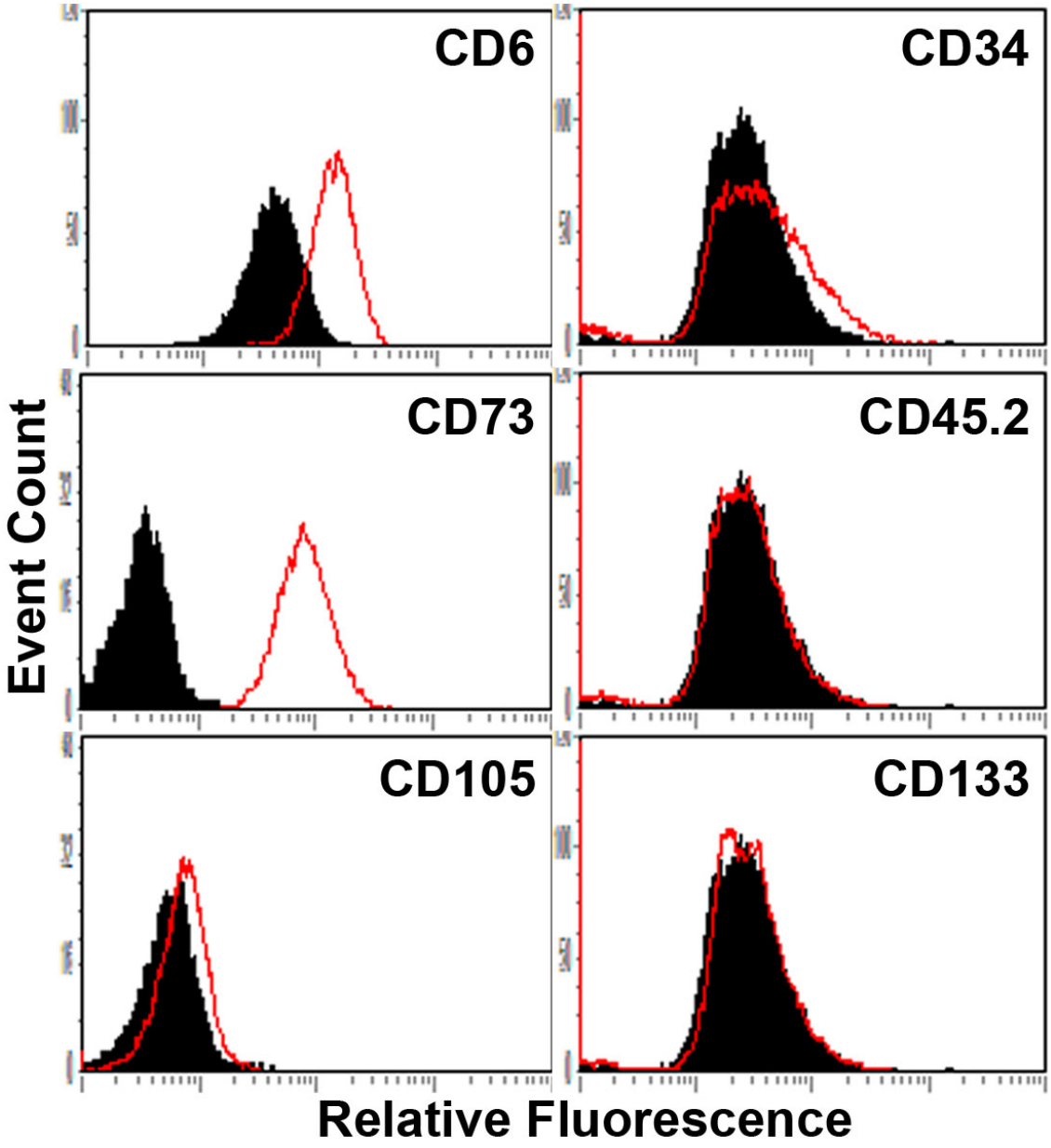


Figure 42: Flow cytometry characterization of Lot . Surface protein expression was assessed at experimental use passage P.6 for three positive markers, CD73, CD105, and CD166, and three negative markers, CD34, CD45, and CD133. Negative markers distinguish MSCs from other marrow-derived and hematopoeitic cell types. CD166 expression was determined using binding to its ligand CD6. Red = stained sample. Black = secondary or cells only control. Note: Weakly positive CD105 signal due to old antibody.

A.2.3 Biochemical Differentiation Results

A.2.3.1 Osteogenic

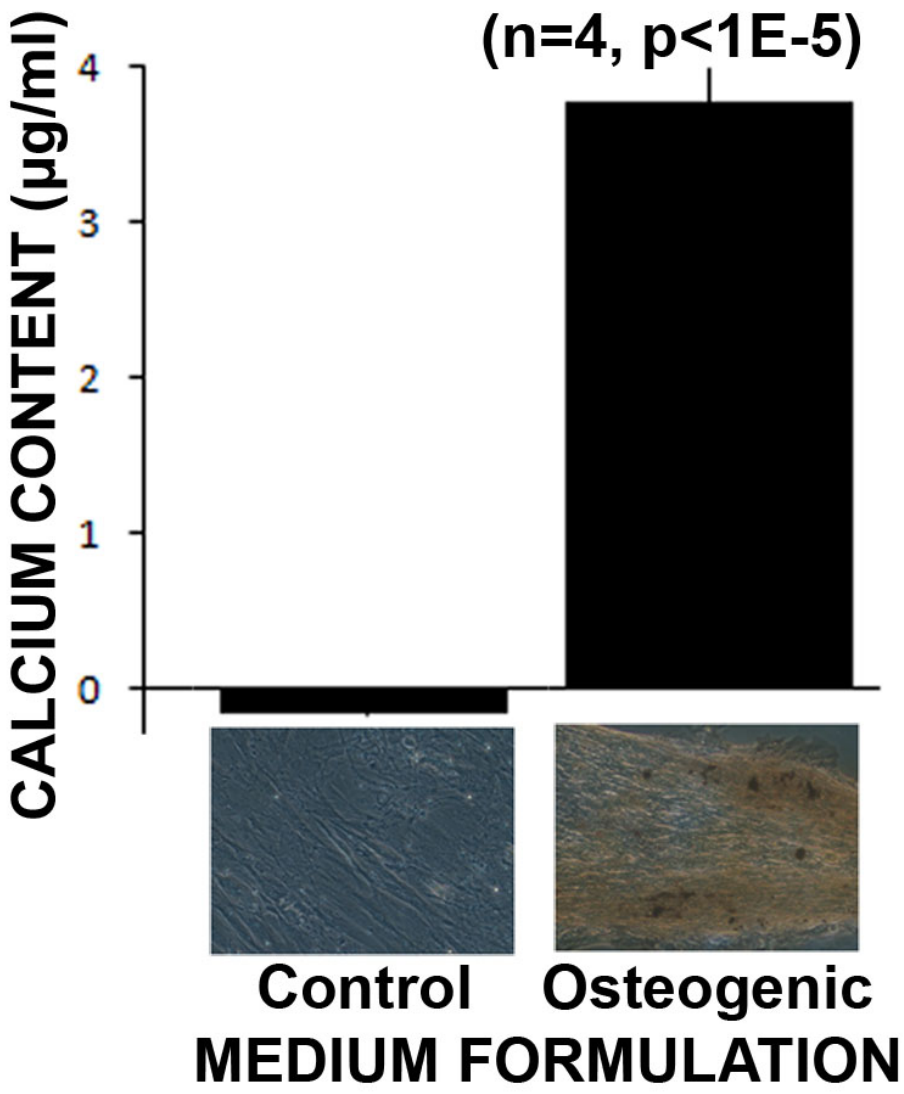


Figure 43: Osteogenic differentiation of Lot . MSCs were cultured in either osteogenic or standard MSC growth media. Deposition of calcium, an indicator of osteogenic differentiation, was assessed qualitatively with von Kossa staining and quantitatively using a Calcium (CPC) LiquiColor test (Stanbio). Nuclei were counterstained with nuclear fast red. Significance was determined using a two-tailed t-test.

A.2.3.2 Adipogenic

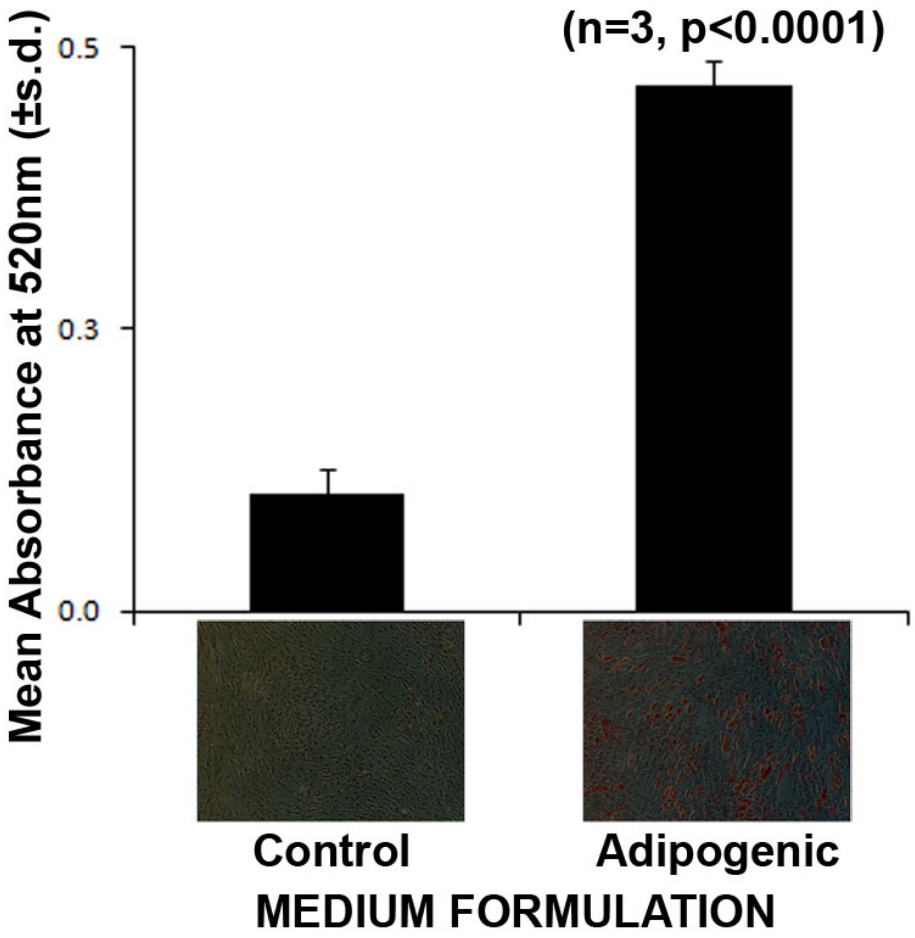


Figure 44: Adipogenic differentiation of Lot . MSCs were cultured in adipogenic or standard MSC growth media. Adipogenic culture media alternated between induction and maintenance media. Adipogenic differentiation was inferred from accumulation of lipid droplets, qualitatively and quantitatively assessed using Oil Red O staining and dye re-suspension, respectively. Nuclei were counterstained with hematoxylin. Significance was determined using a two-tailed t-test. Scale bars = 100μm.

A.3 Methods Development: Mesenchymal Stem Cell PCR Array

In the course of this dissertation, a PCR array to quantify expression of characteristic genes in MSCs was developed in collaboration with SA Biosciences (Frederick, MD). The RT^2 Profiler^{TM} PCR Array Human Mesenchymal Stem Cell is commercially available through SA Biosciences (Catalog number PAHS-082A).

A.3.1 SA Biosciences PCR Array

Mesenchymal Stem Cell PCR Array Gene Table (SA Biosciences)

Position	Unigene	GeneBank	Symbol	Gene Name	Description
A01	Hs.489033	NM_000927	ABCB1	ABC20/CD243	ATP-binding cassette, sub-family B (MDR/TAP), member 1
A02	Hs.591293	NM_001627	ALCAM	CD166/MEMD	Activated leukocyte cell adhesion molecule
A03	Hs.1239	NM_001150	ANPEP	APN/CD13	Alanyl (membrane) aminopeptidase
A04	Hs.480653	NM_001154	ANXA5	ANX5/ENX2	Annexin A5
A05	Hs.502182	NM_001709	BDNF	MGC34632	Brain-derived neurotrophic factor
A06	Hs.654541	NM_199173	BGLAP	BGP/OC	Bone gamma-carboxyglutamate (gla) protein
A07	Hs.73853	NM_001200	BMP2	BMP2A	Bone morphogenetic protein 2
A08	Hs.68879	NM_130851	BMP4	BMP2B/BMP2B1	Bone morphogenetic protein 4
A09	Hs.285671	NM_001718	BMP6	VGR/VGR1	Bone morphogenetic protein 6
A10	Hs.473163	NM_001719	BMP7	OP-1	Bone morphogenetic protein 7
A11	Hs.141125	NM_004346	CASP3	CPP32/CPP32B	Caspase 3, apoptosis-related cysteine peptidase
A12	Hs.502328	NM_000610	CD44	CDW44/CSPG8	CD44 molecule (Indian blood group)
B01	Hs.172928	NM_000088	COL1A1	OI4	Collagen, type I, alpha 1
B02	Hs.1349	NM_000758	CSF2	GMCSF	Colony stimulating factor 2 (granulocyte-macrophage)
B03	Hs.2233	NM_000759	CSF3	G-CSF/GCSF	Colony stimulating factor 3 (granulocyte)
B04	Hs.476018	NM_001904	CTNNB1	CTNNB/DKFZp686D02253	Catenin (cadherin-associated protein), beta 1, 88kDa
B05	Hs.419815	NM_001963	EGF	HOMG4/URG	Epidermal growth factor (beta-urogastrone)
B06	Hs.76753	NM_000118	ENG	CD105/END	Endoglin
B07	Hs.446352	NM_004448	ERBB2	CD340/HER-2	V-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)
B08	Hs.664499	NM_004465	FGF10	FGF10	Fibroblast growth factor 10
B09	Hs.284244	NM_002006	FGF2	BFGF/FGFB	Fibroblast growth factor 2 (basic)
B10	Hs.69747	NM_000148	FUT1	H/HH	Fucosyltransferase 1 (galactoside 2-alpha-L-fucosyltransferase, H blood group)
B11	Hs.390420	NM_002033	FUT4	CD15/ELFT	Fucosyltransferase 4 (alpha (1,3) fucosyltransferase, myeloid-specific)
B12	Hs.647029	NM_003508	FZD9	CD349/FZD3	Frizzled homolog 9 (Drosophila)
C01	Hs.616962	NM_004864	GDF15	GDF-15/MIC-1	Growth differentiation factor 15
C02	Hs.1573	NM_000557	GDF5	BMP14/CDMP1	Growth differentiation factor 5
C03	Hs.492277	NM_001001557	GDF6	BMP13/CDMP2	Growth differentiation factor 6
C04	Hs.447688	NM_182828	GDF7	BMP12	Growth differentiation factor 7
C05	Hs.445977	NM_002097	GTF3A	AP2/TFIIIA	General transcription factor IIIA
C06	Hs.632532	NM_003642	HAT1	KAT1	Histone acetyltransferase 1
C07	Hs.88556	NM_004964	HDAC1	DKFZp686H12203/GON-10	Histone deacetylase 1
C08	Hs.396530	NM_000601	HGF	F-TCF/HGFB	Hepatocyte growth factor (hepapoietin A; scatter factor)
C09	Hs.654455	NM_000545	HNF1A	HNF1/LFB1	HNF1 homeobox A
C10	Hs.643447	NM_000201	ICAM1	BB2/CD54	Intercellular adhesion molecule 1
C11	Hs.856	NM_000619	IFNG	IFG/IFI	Interferon, gamma
C12	Hs.160562	NM_000618	IGF1	IGF1A/IGFI	Insulin-like growth factor 1 (somatomedin C)
D01	Hs.193717	NM_000572	IL10	CSIF/IL-10	Interleukin 10
D02	Hs.126256	NM_000576	IL1B	IL-1/IL1-BETA	Interleukin 1, beta
D03	Hs.654458	NM_000600	IL6	BSF2/IHGF	Interleukin 6 (interferon, beta 2)
D04	Hs.654579	NM_000207	INS	ILPR/IRDN	Insulin
D05	Hs.133397	NM_000210	ITGA6	CD49f/DKFZp686J01244	Integrin, alpha 6
D06	Hs.436873	NM_002210	ITGAV	CD51/DKFZp686A08142	Integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51)
D07	Hs.248472	NM_000887	ITGAX	CD11C/SLEB6	Integrin, alpha X (complement component 3 receptor 4 subunit)
D08	Hs.643813	NM_002211	ITGB1	CD29/FNRB	Integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12)
D09	Hs.224012	NM_000214	JAG1	AGS/AHD	Jagged 1 (Alagille syndrome)
D10	Hs.479756	NM_002253	KDR	CD309/FLK1	Kinase insert domain receptor (a type III receptor tyrosine kinase)
D11	Hs.1048	NM_003994	KITLG	DKFZp686F22250/KL-1	KIT ligand
D12	Hs.2250	NM_002309	LIF	CDF/DIA	Leukemia inhibitory factor (cholinergic differentiation factor)
E01	Hs.599039	NM_006500	MCAM	CD146/MUC18	Melanoma cell adhesion molecule
E02	Hs.166017	NM_000248	MITF	MI/WS2A	Microphthalmia-associated transcription factor
E03	Hs.513617	NM_004530	MMP2	CLG4/CLG4A	Matrix metallopeptidase 2 (gelatinase A, 72kDa gelatinase, 72kDa type IV collagenase)
E04	Hs.527971	NM_006617	NES	Nbla00170	Nestin
E05	Hs.415768	NM_002507	NGFR	CD271/Gp80-LNGFR	Nerve growth factor receptor (TNFR superfamily, member 16)
E06	Hs.495473	NM_017617	NOTCH1	TAN1/hN1	Notch homolog 1, translocation-associated (Drosophila)
E07	Hs.153952	NM_002526	NT5E	CD73/ENT	5'-nucleotidase, ecto (CD73)
E08	Hs.558459	NM_007083	NUDT6	ASFGF2/FGF-2	Nudix (nucleoside diphosphate linked moiety X)-type motif 6
E09	Hs.533055	NM_003884	KAT2B	CAF/P	K(lysine) acetyltransferase 2B
E10	Hs.509067	NM_002609	PDGFRB	CD140B/JTK12	Platelet-derived growth factor receptor, beta polypeptide
E11	Hs.462550	NM_033198	PIGS	DKFZp686K20216	Phosphatidylinositol glycan anchor biosynthesis, class S
E12	Hs.249184	NM_002701	POU5F1	OCT3/OCT4	POU class 5 homeobox 1
F01	Hs.162646	NM_015869	PPARG	CIMT1/NR1C3	Peroxisome proliferator-activated receptor gamma
F02	Hs.614734	NM_006017	PROM1	AC133/CD133	Prominin 1
F03	Hs.395482	NM_005607	PTK2	FADK/FAK	PTK2 protein tyrosine kinase 2
F04	Hs.654514	NM_002838	PTPRC	B220/CD45	Protein tyrosine phosphatase, receptor type, C
F05	Hs.247077	NM_001664	RHOA	ARH12/ARHA	Ras homolog gene family, member A
F06	Hs.535845	NM_004348	RUNX2	AML3/CBFA1	Runt-related transcription factor 2
F07	Hs.597422	NM_012434	SLC1A5	AST/ISSD	Solute carrier family 17 (anion/sugar transporter), member 5
F08	Hs.75862	NM_005359	SMAD4	DPC4/JIP	SMAD family member 4
F09	Hs.189329	NM_020429	SMURF1	KIAA1625	SMAD specific E3 ubiquitin protein ligase 1
F10	Hs.705442	NM_022739	SMURF2	DKFZp686F0270	SMAD specific E3 ubiquitin protein ligase 2
F11	Hs.518438	NM_003106	SOX2	ANOP3/MCOPS3	SRY (sex determining region Y)-box 2
F12	Hs.647409	NM_000346	SOX9	CMD1/CMPD1	SRY (sex determining region Y)-box 9
G01	Hs.381715	NM_181486	TBX5	HOS	T-box 5
G02	Hs.492203	NM_198253	TERT	EST2/TCS1	Telomerase reverse transcriptase
G03	Hs.645227	NM_000660	TGFB1	CED/DPD1	Transforming growth factor, beta 1
G04	Hs.592317	NM_003239	TGFB3	ARVD/TGF-beta3	Transforming growth factor, beta 3
G05	Hs.644697	NM_006288	THY1	CD90	Thy-1 cell surface antigen
G06	Hs.241570	NM_000594	TNF	DIF/TNF-alpha	Tumor necrosis factor (TNF superfamily, member 2)
G07	Hs.109225	NM_001078	VCAM1	CD106/DKFZp779G2333	Vascular cell adhesion molecule 1
G08	Hs.73793	NM_003376	VEGFA	MVCD1/VEGF	Vascular endothelial growth factor A
G09	Hs.642813	NM_003380	VIM	FLJ36605	Vimentin
G10	Hs.440848	NM_000552	VWF	F8VWF/VWD	Von Willebrand factor
G11	Hs.336930	NM_031131	WNT3A	MGC119418	Wingless-type MMTV integration site family, member 3A
G12	Hs.335787	NM_174900	ZFP42	REX1/ZNF754	Zinc finger protein 42 homolog (mouse)
H01	Hs.534255	NM_004048	B2M	B2M	Beta-2-microglobulin
H02	Hs.412707	NM_000194	HPRT1	HGPRT/HPRT	Hypoxanthine phosphoribosyltransferase 1
H03	Hs.523185	NM_012423	RPL13A	RPL13A	Ribosomal protein L13a
H04	Hs.592355	NM_002046	GAPDH	G3PD/GAPD	Glyceraldehyde-3-phosphate dehydrogenase
H05	Hs.520640	NM_001101	ACTB	PS1TP5BP1	Actin, beta
H06	N/A	SA_00105	HGDC	HIGX1A	Human Genomic DNA Contamination
H07	N/A	SA_00104	RTC	RTC	Reverse Transcription Control
H08	N/A	SA_00104	RTC	RTC	Reverse Transcription Control
H09	N/A	SA_00104	RTC	RTC	Reverse Transcription Control
H10	N/A	SA_00103	PPC	PPC	Positive PCR Control
H11	N/A	SA_00103	PPC	PPC	Positive PCR Control
H12	N/A	SA_00103	PPC	PPC	Positive PCR Control

APPENDIX B

DETAILED PROTOCOLS

B.1 Protein Coating of Cell Culture Surfaces

1. Make a sterile diluted extracellular matrix protein solution at desired concentration (typically 5μg/cm^2 or 1% w/v for gelatin) using manufacturer-recommended solvent. Mix solution well.

2. To sterile surfaces on which cells are to be seeded, add diluted protein coating solution (3 ml/10 cm^2 seeding ring for strain MHC or 2 ml/28.5 cm^2 for parallel plate glass slides).

3. Allow protein to adsorb to surface at 37°C for 2 hours. (For glass slides that are difficult to move, let sides sit for 30 minutes, flip horizontally 180°, sit again for 30 minutes.)

4. Aspirate protein coating solution. Immediately seed cells at desired concentration (cells/cm^2).

B.2 Application of Equibiaxial Cyclic Strain

Day 1: Preparation

Estimated time: 4 hours

1. UV spacers 30 on each side in UV box in hood.
2. Prepare membrane holder chambers (MHCs), wearing gloves the entire time.
3. Etch silicone membranes 20 with 1N H_2SO_4 (diluted with milliQ or nanopure H_2O) in chemical hood.
4. Wash both sides well with dH_2O, keeping track of etched side. Tip: Place etched side facing right palm or, if putting piece down, etched side faces up.
5. Autoclave all supplies.
    - Glass dishes, 150 mm glass petri 1 dish/MHC
    - MHCs 1 per sample; for each group, need at least 1 static and 1 strain. Max. 16 MHCs.
    - Paper inserts 1/MHC on which to put MHC so that silicone doesnt stick to glass petri dish.
    - Metal tray useful for transferring dishes back and forth between hood and incubator.
    - Instruments as needed. At least two pairs of forceps are required (long thin, curved ones for manipulating seeding rings and large, heavy duty ones for moving MHCs onto glass dish).

Day 2: Cell Seeding

Estimated Time: 4 hours

1. Prepare coating solution.
2. Image cells before trypsinizing.

3. Record desired length of static incubation, actual start time, actual stop time.

Day 3:

No tasks.

Day 4: Application of strain

Estimated Time: 4 hours

1. Image cells before putting on strain device (t=0 pictures).
2. Transfer 1 MHC to the equibiaxial strain device (maximum of 4/experiment), threading MHC into one of the four available slots. For each MHC subjected to strain, transfer 1 MHC to the same incubator and leave the MHC in the petri dish for continued static control culture.
3. Record desired magnitude, desired frequency, desired length of strain (protocol written as if 48 hr static/strain desired), actual start time, and actual stop time.

Day 5:

No tasks.

Day 6: Stop strain

1. Remove samples from bioreactor.
2. Image samples and/or harvest cells, depending on desired experimental assessments.

B.3 Application of Steady Laminar Fluid Shear Stress

This protocol employs parallel plate shear chambers to apply shear stress to monolayers of cells seeded on glass slides. Day 1: Prepare for shear

1. UV spacers 30 on each side in UV box in hood. Store in sterile location until ready to use.

2. Autoclave all supplies.

    - Shear blocks (base, top, rubber gasket)
    - Flow loops (media reservoir, tubing, pulse dampener, tubing with double luer entry point for shear block)
    - Glass slides 28.5 cm^2 slides for flow block
    - Metal tray useful for adding blocks into flow loop on sterile surface and for transferring loops between hood and incubator.
    - Instruments as needed. Three pairs of forceps (at least two long-handled), one pair slide forceps, one pair forceps.

Day 2: Seed cells

1. Place 1-2 glass slides in a square petri dish up to total number of slides needed.

2. Protein coat glass slides as described above.

3. Trypsinize cells and concetrate to desired cells/ml density. Assume 1 ml seeding volume of 28.5 cm^2. MSCs and ECs seeded at 10,000 cells/cm^2.

4. Seed cells in 1 ml volume for 20 min on each side at room temperature, flipping slides horizontally 180°.

5. Add culture media up to 20 ml total volume per square dish. Move dishes to 37°C incubator.

Day 3:

No work.

Day 4: Set up shear

For each flow loop (1 per shear sample):

1. Construct flow loop in sterile environment.
2. Add 125 ml culture media per loop.
3. Prewarm media in flow loop by running on pulsatile pump in large incubator without shear block attached.
4. Prepare shear block under sterile conditions: base, rubber gasket, slide seeded with cells, spacer, top, and then add 6 screws. Be sure to tighten screws in consistent alternating fashion (e.g., top right, bottom left, top left, bottom right, top middle, bottom middle) so that shear block series is tightened uniformly.
5. Transfer flow loop with shear block to incubator. Begin pulsatile flow at speed (rpm) predetermined for each flow block to equate to desired theoretical shear stress across slide (e.g., 44 rpm 15 dyn/cm^2 for some McMaster-Carr pulsatile pumps).
6. Incubate blocks at 37°C for desired duration of shear stress. Check blocks frequently to ensure no leaks.
7. Parallel static samples are placed in 125ml prewarmed media in 15 mm petri dish and kept in same incubator for duration of shear.

Day 5: Take down shear

1. Assuming a 24 hour applied shear (or modify, as needed), take 1 static and 1 shear sample down at the same time. Obtain slide from flow block using reverse of set-up procedure.
2. Phase image slides.

3. Harvest or fix cells as desired, depending on assessment.

4. Wash all parts of shear system at least 2x each side/port. Let parts hang to air dry. Be sure flow blocks not scratched at any point. Avoid crimping of tubing during storage.

B.4 Gene Expression Assessment

B.4.1 RNA Isolation

Protocol modified from Qiagen RNeasy Mini Isolation kit (Cat. No. 74104).

Reagents and supplies:

- RNeasy Mini Isolation kit - Qiagen 74104
- Qiashredders - Qiagen 79654
- RNase-free DNase Kit - Qiagen 79254
- RNase/DNase Free Water - Sigma W-4502
- RNase/DNase free B-mercaptoethanol - Sigma M3148
- Ethanol molecular biology grade - Sigma E702-3
- RNase/DNase free tubes
- Clean forceps to remove tubes from bag

Working Solutions

- Lysis Buffer (from RNeasy kit): Mix RLT buffer (10mL) with 100 μL B-ME. Protect from light and store at RT for up to one month.
- RPE Buffer Solution (from RNeasy kit): Add 4 volumes of ethanol (96-100%), per instructions on bottle
- DNase Stock (DO NOT VORTEX): Mix lyophilized DNase powder with 550 μl water in kit to get DNase stock solution then aliquot 100 μl. Mix by inverting DO NOT VORTEX. Store at -20°C for up to 9 mo. Once thawed, store at 4°C for up to 6 weeks. Do not refreeze.
- 70% Ethanol: Mix 200 proof ethanol for molecular biology with RNase/DNase Free Water. Store at RT.

Method:

Work can be done on any bench. Clean surfaces with dehydration alcohol or RNase Away. Use clean, well-calibrated pipetmans with barrier pipet tips. All steps are at room temperature. Wear gloves at all times. Record data, experiment number, and samples isolated.

Prepare cells

1. As quickly as possible, obtain a cell pellet and put on ice. [Wash, trypsin, quench, spin, aspirate, continue with lysis below.]

Lyse Cells

1. Loosen cell pellets and add 350 μl of lysis buffer to each tube. Mix well.
2. Transfering mixture to Qiashredder column and spin in centrifuge at max (10,000 RPM) for 2 minutes to homogenize lysate. (This can be done after freezing, if prefer.)
3. Freeze at -70°C until ready to isolate RNA.

Isolate RNA

Record date.

1. Prepare DNase mix. 10 μl to 70 μl RDD for 80 μl/sample. (Make 1 sample extra.)
2. Warm samples at 37°C for 10 minutes
3. Add 350 l of 70% ethanol and mix well by pipetting.
4. Transfer the 700 μl to RNeasy mini column. Optional: If prefer, can rerun effluent back through column to max RNA binding.
5. Centrifuge at 14,000 rcf for 1 min. Discard flow through.
6. DNase Treatment
    - Add 350 μl RW1 solution to RNeasy column.
    - Centrifuge at 14,000 rcf for 1 min. Discard flow through.

- Add 80 μl of DNase solution directly to membrane and incubate at RT for 15 min.
- Add 350 μl RW1 solution to RNeasy column.
- Centrifuge at 14,000 rcf for 1 min. Discard flow through.

7. Add 700 μl RW1 solution to RNeasy column.
8. Centrifuge at 10,000 RPM for 30 sec. Discard flow through.
9. Add 500 μl of RPE Buffer.
10. Centrifuge at 14,000 rcf for 1 min. Discard flow through.
11. Add another 500 μl of RPE buffer.
12. Centrifuge at 14,000 rcf for 2 min. Discard flow through.
13. Place column in new 2 ml tube (supplied) and centrifuge column empty for 1 min.
14. Place the columns in the 1.5 ml tubes.
15. Add 30 μl of RNase free water and incubate for 1 min at RT
16. Centrifuge at 14,000 rcf for 1 min.
17. Discard the columns and place the samples on ice or freeze at -70°C until ready to use RNA. (Try to spec on Nanodrop and/or run bioanalyzer on this day and then freeze. Thaw to continue.)

B.4.2 cDNA Synthesis for PCR Arrays

Protocol is based on SA Biosciences First Strand cDNA synthesis kit (Cat. No. C-03). cDNA is synthesized using the SA Biosciences kit in order to be able to use positive PCR controls included on the PCR arrays.

1. Briefly (10-15 seconds) spin down all reagents.
2. Prepare the Genomic DNA Elimination Mixture:
   - **a** For each RNA sample, combine the following in a sterile PCR tube:
     - 25.0 ng to 5.0 μg total RNA
     - 2.0 μl GE** (5X gDNA Elimination Buffer)
     - H_2O to a final volume of 10.0 μl
   - **b** Mix the contents gently with a pipettor followed by brief centrifugation.
   - **c** Incubate at 42°C for 5 min.
   - **d** Chill on ice immediately for at least one minute.
   - **e** Prepare the RT Cocktail:

     RT Cocktail 1 reaction
     - 4 μl BC3 (5X RT Buffer 3)
     - 1 μl P2 (Primer & External Control Mix)
     - 2 μl RE3 (RT Enzyme Mix 3)
     - 3 μl H_2O
     - 10 μl Final Volume
3. First Strand cDNA Synthesis Reaction:
   - **a** Add 10 μl of RT Cocktail to each 10-μl Genomic DNA Elimination Mixture.
   - **b** Mix well but gently with a pipettor.
   - **c** Incubate at 42°C for exactly 15 min and then immediately stop the reaction by heating at 95°C for 5 minutes.

d Add 91 μl of H2O to each 20-μl of cDNA synthesis reaction. Mix well.

e Hold the finished First Strand cDNA Synthesis Reaction on ice until the next step or store overnight at -20°C.

B.4.3 cDNA Synthesis for Standard qPCR

The following procedure is designed to convert 1 pg to 5 μg of total RNA or 1 pg to 500 ng of poly(A)+ RNA into first-strand cDNA. Protocol modified from Invitrogen First-Strand cDNA Synthesis kit (Cat. No: 18080-051).

1. Mix and briefly centrifuge each component before use.
2. Combine the following in a 0.2- or 0.5-ml tube:
   Component Amount
   - n μl up to 5 μg total RNA
   - 1 μl 50 μM oligo(dT)20 primer
   - 1 μl 50 ng/μl random hexamers primer
   - 1 μl 10 mM dNTP mix
   - DEPC-treated water to 10 μl
3. Incubate at 65°C for 5 min, then place on ice for at least 1 min.
4. Prepare the following cDNA Synthesis Mix, adding each component in the indicated order.
   Component
   - 2 μl 10X RT buffer
   - 4 μl 25 mM MgCl2
   - 2 μl 0.1 M DTT
   - 1 μl RNaseOUT (40 U/μl)
   - 1 μl SuperScript III RT (200 U/μl)
5. Add 10 μl of cDNA Synthesis Mix to each RNA/primer mixture, mix gently, and collect by brief centrifugation. For a reaction primed with random hexamers and oligodT, incubate tubes 10 min at 25°C, followed by 50 min at 50°C.

6. Terminate the reactions at 85°C for 5 min. Chill on ice.

7. Collect the reactions by brief centrifugation. Add 1 μl of RNase H to each tube and incubate for 20 min at 37°C.

8. cDNA synthesis reaction can be stored at -20°C or used for PCR immediately.

B.4.4 Gene Expression Quantification

B.4.4.1 Standard qPCR

This protocol assumes use of Applied Biosystems Power 2x SYBR Green mastermix (Cat. No. 4309155).

1. Prepare standard curve solutions, using nine 1/10 serial dilutions of initial concentrated standard solution.

2. For each well, aliquot 1 μl template, forward and reverse primers to desired final concentration (e.g., 800 nM), 12.5 μl 2x Power SYBR Green mastermix, and H_2O up to 25 μl.

3. Once PCR plate loaded, cover wells with clear film covers. Spin plate briefly to ensure liquid is located at the base of each well.

4. Run plate on ABI Step One Plus qRT-PCR machine, using default protocol.

5. Analyze qRT-PCR results in ABI Step One Plus software.

B.4.4.2 PCR Array

This protocol is based on SA Biosciences PCR Array instructions.

1. Briefly (10-15 seconds) spin down all reagents.

2. Experimental Cocktail Preparation (for Custom PCR Arrays & Plate H (BioMark) PCR Arrays, see NOTES below). Mix the following components in a 5-ml tube or a multi-channel reservoir:
   96-well Plate Format, Plate Format Designation A,C,D, or F:

   - 1350 μl 2X SABiosciences RT2 qPCR Master Mix
   - 102 μl Diluted First Strand cDNA Synthesis Reaction
   - 1248 μl H_2O
   - 2700 μl Total Volume

B.4.4.3 cDNA Microarray

Agilent whole human genome microarrays were run at the Morehouse School of Medicine microarray core facility. Contact person: Dr. Leonard Anderson.

- Briefly, RNA samples were analyzed for RNA quality using a Bioanalyzer.
- Samples were labeled and hybridized to microarrays using a one-color reaction.
- Microarray images were captured using Feature Extraction. Quality control of microarray images was completed in Feature Extraction, prior to exporting intensity data per probe spot.
- Intensity data per probe spot for all microarrays were analyzed using GeneSpring software.

B.4.5 Protein Expression Quantification

B.4.5.1 Flow Cytometry

Reagents:

- 4% Formaldehyde - Dilute 10% ultrapure formaldehyde with sterile filtered PBS with Ca and Mg.
- Working Buffer Solution (WBS) - Dilute 0.3 g BSA in 100 ml PBS. Add 1 μl Tween-20 per 100 ml WBS. Store at 4°C.
- Blocking solution (Serum of secondary antibody donor species): 1:10 dilution of serum to working buffer solution.
- Permeabilitizing solution (0.5% Triton): 1 ml of 100% Triton diluted in 200 ml sterile water. Store at 4°C.
- Fixing solution (4% Formaldehyde): Dilute 20% Formaldehyde in sterile filtered PBS with Ca and Mg in a 1 part:3 part ratio.

Prepare cells for flow cytometry:

1. Phase image cells at 5x for record keeping purposes.
2. Wash t75 flask in 6 ml DPBS.
3. Trypsinize cells with 3 ml at 37°C for 3 min.
4. Gently tap flask to dislodge remaining adherent cells. Quench with 9ml cell culture medium. Pipet up and down to remove remaining adherent cells.
5. Transfer 12ml to 15ml Falcon tube. Pellet cells by centrifuging 5 min at 200 rcf.
6. Aspirate supernatant. Resuspend in 4 ml 4% paraformaldehyde. Fix 15 min at 4°C, mixing occasionally with gentle flicking of tube.
7. Add 4ml WBS (working buffer solution; not more than 1 month old, ideally). Homogenize well.

8. Take 100ul for Coulter Count measurement of cell number.
9. Pellet cells spin 5 min at 200 rcf.
10. Calculate cell number per flask.
11. Resuspend in WBS with appropriate volume to prepare for flow cytometry.
12. Store at 4°C until ready to proceed with flow cytometry staining.

Stain cells and image for flow cytometry:

1. PREPARE CELLS: Wash, trypsinize, and quench cells as normal.
2. PELLET: Spin 5 min at 1000 rpm. Aspirate supernatant.
3. FIX: Add 4 ml 4% formaldehyde for 15 min at 4°C.
4. PELLET: Dilute with working buffer solution, centrifuge and aspirate.
5. PERMEABILIZE: (For intracellular markers only) Add 2 ml of permeabilizing solution for 30 min (vortex every 15 min to prevent cell settling) at 4°C.
    - PELLET: (Intracellular markers only.) Dilute w/ working buffer solution, centrifuge and aspirate.
6. BLOCK: Add 1 ml of blocking solution for 1 hr (vortex every 15 min to prevent cell settling).
7. PELLET: Dilute with working buffer solution, centrifuge and aspirate.
8. STAINING PREPARATION: Add 400 μl of working buffer solution and split tubes if appropriate.
9. PRIMARY STAINING: To all tubes, except controls, add primary antibody in 400ul (optimized dilution amount). Incubate at 4°C for 30 min.
10. PELLET: Dilute w/ working buffer solution, centrifuge and aspirate.

11. SECONDAY STAINING: To all tubes, except appropriate controls, add secondary antibody (optimized dilution amount). Incubate at 4°C for 30 min.

12. PELLET: Dilute w/ working buffer solution, centrifuge, and aspirate.

13. WASH: Add 1 ml working buffer solution, centrifuge and aspirate.

14. FINAL SAMPLE PREPARATION: Reconstitute all tubes to 0.5 ml with working buffer solution. Filter to remove particles $\geq$0.5μm using blue-capped filter sterilizing test tubes.

15. Run samples on BD LSR. Normalize FSC and SS voltages to ensure the cell population falls within the scale. Normalize fluor voltage to ensure signal is distributed across the range of standard bead intensities. Record voltage settings. Measure all samples.

B.4.5.2 Immunocytochemistry

Basic immunostain protocol for monolayer cells:

1. Wash slides with PBS (3 x 5 min in excess PBS)
2. Permeabilize if needed (if antigen is intracellular and/or if you want to use a nuclear counterstain) (0.05% triton-x detergent solution used for cell monolayers; incubate at RT. For tissue sections, can boil in sodium citrate solution to unmask antigen (e.g., using a pressure cooker).
3. Wash well with PBS. (3 x 5 min in excess PBS)
4. Pap pen [hydrophobic barrier pen, e.g., available from Vector Labs, etc.] around section (can be done during PBS washes or, if crunched for time, after the block step). Be sure pap pen holds liquid within boundary well.
5. Block with 5% serum in PBS, using serum from the species in which your secondary antibody was made.
6. There is no need to wash between block and primary, since these are in the same diluent.
7. Primary incubation. Use as little volume as possible so you are confident sample is uniformly covered, but that you dont need to waste any primary antibody. In Nerem lab, 1/100 standard primary dilution often used; can get better staining and resulting images though (and save on antibody use) by optimizing the dilution used. (2 hr at RT or o/n at 4°C)
8. Wash well. (3 x 5 min in excess PBS)
9. Secondary incubation. Standard AlexaFluor secondaries can be diluted 1/100. Nuclear counterstain such as DAPI or Hoechst 33258 can be included at this time. 1/1000 works ok if you want only dull Hoechst counterstain; for brighter counterstain, use $\tilde{1}$/200 dilution. (1 hr at RT)

10. Wash well. (3 x 5 min in excess PBS)

11. Remove pap pen with clean, sharp razor blade.

12. Coverslip. Add coverslipping media. Add coverslip (If using confocal imaging, make sure you have thin coverslips on, otherwise, focal plane will be in coverslip rather than in area of cells.). Use forceps to push out any air bubbles trapped between slide and cover slip.

13. Image (fluorescence: confocal, multi-photon confocal, histology; brightfield: histology)

14. If desired, after slides have dried completely, nailpolish around the outside of the coverslip area to ensure further evaporation doesnt happen.

15. Store fluorescent-stained slides at 4°C. Store visible light-stained slides at RT.

APPENDIX C

SUPPORTING DOCUMENTATION: MESENCHYMAL STEM CELLS REARRANGE INTO MULTICELLULAR CLUSTERS IN RESPONSE TO EQUIBIAXIAL CYCLIC STRAIN

For additional information on the response of MSCs to applied equibiaxial cyclic strain, please refer to:

Doyle, A.M. textitet al). underlineHuman mesenchymal stem cells form multicellular structures in response to applied cyclic strain. Ann Biomed Eng. 2009. Apr; 37(4):783-93. [67]

This study describes cellular rearrangements of MSCs into multicellular 'knobs' or 'clusters' with 48 hours applied cyclic strain (10%, 1 Hz) on gelatin-coated silicone. No marked changes in cytoskeletal filament expression or organization were visible in samples exposed to strain, suggesting other signal transduction mechanisms may regulate multicellular structure formation. This finding motivated subsequent MSCs and SMCs comparative signaling studies (Chapers 3 and 4), to better determine which networks are involved in MSCs response to cyclic strain. Doyle et al also demonstrated the dependence of MSCs response to cyclic strain on the underlying protein substrate. Dependence of cell mechanoresponse on underling protein substrate was also observed in MSCs exposed to applied shear stress (Figure 28).

APPENDIX D

MICROARRAY SUPPLEMENTAL TABLES

D.1 Cyclic Strain-Responsive Microarrays

D.1.1 Conserved Strain-Responsive Genes

Table 14: Genes with conserved strain-responses in MSCs and SMCs. 442 genes were significantly ($p < 0.05$) strain-responsive according to ANOVA force-dependence, SMC paired t-test, and MSC paired t-test calculations. Genbank accession numbers, gene descriptions, chromosome locations, and Gene Ontology categorizations are listed for each conserved strain-responsive gene.

ProbeName	Common name	Gene Symbol	Genbank Accession	Description	Chromosome Number (Avadis)	GO biological process	GO cellular component	GO molecular function
A_23_P107116	NM_007148	ZNF179	NM_007148	Homo sapiens zinc finger protein 179 (ZNF179), mRNA [NM_007148]	chr17	GO:0006512(ubiquitin cycle);GO:0006955(immune response)		GO:0003924(GTPase activity);GO:0005515(protein binding);GO:0005525(GTP binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P131375	NM_152391	PQLC3	NM_152391	Homo sapiens PQ loop repeat containing 3 (PQLC3), mRNA [NM_152391]	chr2		GO:0016020(membrane);GO:0016021(integral to membrane)	
A_23_P29994	NM_203284	RBPJ	NM_203284	Homo sapiens recombination signal binding protein for immunoglobulin kappa J region (RBPJ), transcript variant 4, mRNA [NM_203284]	chr4	GO:0006310(DNA recombination);GO:0006350(transcription);GO:0006366(transcription from RNA polymerase II promoter);GO:0007219(Notch signaling pathway);GO:0045892(negative regulation of transcription, DNA-dependent)	GO:0005634(nucleus);GO:0005730(nucleolus)	GO:0000150(recombinase activity);GO:0003700(transcription factor activity);GO:0003702(RNA polymerase II transcription factor activity);GO:0005515(protein binding)
A_24_P127051	A_24_P127051	A_24_P127051			chr6			
A_23_P145584	NM_003344	UBE2H	NM_003344	Homo sapiens ubiquitin-conjugating enzyme E2H (UBC8 homolog, yeast) (UBE2H), transcript variant 1, mRNA [NM_003344]	chr7	GO:0006464(protein modification process);GO:0006511(ubiquitin-dependent protein catabolic process);GO:0006512(ubiquitin cycle)		GO:0004842(ubiquitin-protein ligase activity);GO:0016874(ligase activity);GO:0019787(small conjugating protein ligase activity)
A_23_P151506	NM_016445	PLEK2	NM_016445	Homo sapiens pleckstrin 2 (PLEK2), mRNA [NM_016445]	chr14	GO:0007242(intracellular signaling cascade);GO:0030036(actin cytoskeleton organization and biogenesis)	GO:0005856(cytoskeleton);GO:0016020(membrane)	
A_23_P31073	NM_005375	MYB	NM_005375	Homo sapiens v-myb myeloblastosis viral oncogene homolog (avian) (MYB), mRNA [NM_005375]	chr6	GO:0006355(regulation of transcription, DNA-dependent);GO:0006397(mRNA processing);GO:0007049(cell cycle);GO:0008380(RNA splicing);GO:0045449(regulation of transcription)	GO:0005634(nucleus);GO:0005681(spliceosome);GO:0016363(nuclear matrix)	GO:0003677(DNA binding);GO:0005515(protein binding);GO:0016563(transcriptional activator activity);GO:0030528(transcription regulator activity)
A_23_P250982	NM_016048	ISOC1	NM_016048	Homo sapiens isochorismatase domain containing 1 (ISOC1), mRNA [NM_016048]	chr5	GO:0008152(metabolic process)	GO:0005777(peroxisome)	GO:0003824(catalytic activity)
A_24_P29595	NM_139244	STXBP5	NM_139244	Homo sapiens syntaxin binding protein 5 (tomosyn) (STXBP5), mRNA [NM_139244]	chr6	GO:0015031(protein transport);GO:0016192(vesicle-mediated transport)	GO:0016020(membrane);GO:0016021(integral to membrane)	
A_23_P84952	NM_006521	TFE3	NM_006521	Homo sapiens transcription factor binding to IGHM enhancer 3 (TFE3), mRNA [NM_006521]	chrX	GO:0006355(regulation of transcription, DNA-dependent);GO:0006366(transcription from RNA polymerase II promoter)	GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0005515(protein binding)
A_24_P319736	NM_002398	MEIS1	NM_002398	Homo sapiens Meis homeobox 1 (MEIS1), mRNA [NM_002398]	chr2	GO:0006355(regulation of transcription, DNA-dependent);GO:0007275(multicellular organismal development)	GO:0005634(nucleus);GO:0005667(transcription factor complex)	GO:0003705(RNA polymerase II transcription factor activity, enhancer binding);GO:0005515(protein binding)
A_23_P116414	NM_007069	HRASLS3	NM_007069	Homo sapiens HRAS-like suppressor 3 (HRASLS3), mRNA [NM_007069]	chr11	GO:0007049(cell cycle);GO:0008150(biological_process);GO:0045786(negative regulation of progression through cell cycle)	GO:0005575(cellular_component);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0003674(molecular_function);GO:0005515(protein binding)
A_23_P94533	NM_001912	CTSL1	NM_001912	Homo sapiens cathepsin L1 (CTSL1), transcript variant 1, mRNA [NM_001912]	chr9	GO:0006508(proteolysis)	GO:0005576(extracellular region);GO:0005764(lysosome)	GO:0004197(cysteine-type endopeptidase activity);GO:0004217(cathepsin L activity)
A_24_P68908	BX640843	LOC344887	BX640843	Homo sapiens mRNA; cDNA DKFZp686B14224 (from clone DKFZp686B14224). [BX640843]	chr3			
A_24_P133253	NM_000899	KITLG	NM_000899	Homo sapiens KIT ligand (KITLG), transcript variant b, mRNA [NM_000899]	chr12	GO:0007155(cell adhesion);GO:0007165(signal transduction);GO:0008283(cell proliferation);GO:0009887(organ morphogenesis);GO:0030097(hemopoiesis)	GO:0005886(plasma membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005173(stem cell factor receptor binding);GO:0005515(protein binding);GO:0008083(growth factor activity)
A_24_P672240	ENST00000380682	FRMPD4		PDZ domain containing 10 [Source:RefSeq_peptide;Acc:NP_055543] [ENST00000380682]	chrX		GO:0005856(cytoskeleton)	GO:0005515(protein binding)
A_23_P83110	NM_018249	CDK5RAP2	NM_018249	Homo sapiens CDK5 regulatory subunit associated protein 2 (CDK5RAP2), transcript variant 1, mRNA [NM_018249]	chr9	GO:0007420(brain development);GO:0045664(regulation of neuron differentiation)	GO:0005813(centrosome);GO:0005856(cytoskeleton)	GO:0008017(microtubule binding);GO:0042808(neuronal Cdc2-like kinase binding)
A_23_P13740	NM_014903	NAV3	NM_014903	Homo sapiens neuron navigator 3 (NAV3), mRNA [NM_014903]	chr12			GO:0000166(nucleotide binding);GO:0005524(ATP binding);GO:0017111(nucleoside-triphosphatase activity)
A_23_P57089	NM_020182	TMEPAI	NM_020182	Homo sapiens transmembrane, prostate androgen induced RNA (TMEPAI), transcript variant 1, mRNA [NM_020182]	chr20	GO:0030521(androgen receptor signaling pathway)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0003674(molecular_function);GO:0005515(protein binding)
A_23_P128574	NM_017993	ENOX1	NM_017993	Homo sapiens proliferation-inducing protein 38 (PIG38), mRNA [NM_017993]	chr13			GO:0000166(nucleotide binding);GO:0003676(nucleic acid binding)
A_32_P96752	AW946823	AW946823	AW946823	AW946823 RC2-ET0022-080500-012-b10 ET0022 Homo sapiens cDNA, mRNA sequence [AW946823]	chr6			
A_23_P82868	NM_000930	PLAT	NM_000930	Homo sapiens plasminogen activator, tissue (PLAT), transcript variant 1, mRNA [NM_000930]	chr8	GO:0006464(protein modification process);GO:0006508(proteolysis);GO:0007596(blood coagulation)	GO:0005576(extracellular region)	GO:0008233(peptidase activity);GO:0008243(plasminogen activator activity)
A_23_P14458	NM_144581	C14orf149	NM_144581	Homo sapiens chromosome 14 open reading frame 149 (C14orf149), mRNA [NM_144581]	chr14			
A_24_P344961	NM_133265	AMOT	NM_133265	Homo sapiens angiomotin (AMOT), mRNA [NM_133265]	chrX	GO:0030036(actin cytoskeleton organization and biogenesis);GO:0045766(positive regulation of angiogenesis)	GO:0005884(actin filament);GO:0005923(tight junction);GO:0030027(lamellipodium);GO:0031410(cytoplasmic vesicle)	
A_23_P152505	NM_020686	ABAT	NM_020686	Homo sapiens 4-aminobutyrate aminotransferase (ABAT), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA [NM_020686]	chr16	GO:0007610(behavior);GO:0009450(gamma-aminobutyric acid catabolic process);GO:0042135(neurotransmitter catabolic process);GO:0048148(behavioral response to cocaine)	GO:0005739(mitochondrion)	GO:0003867(4-aminobutyrate transaminase activity);GO:0016740(transferase activity);GO:0030170(pyridoxal phosphate binding);GO:0042803(protein homodimerization activity);GO:0047298((S)-3-amino-2-methylpropionate transaminase activity)

A_32_P38637	NM_032534	KRBA1	NM_032534	Homo sapiens KRAB-A domain containing 1 (KRBA1), mRNA [NM_032534]	chr7	GO:0006355(regulation of transcription, DNA-dependent)	GO:0005622(intracellular)	GO:0003676(nucleic acid binding)
A_23_P81811	NM_080604	TJAP1	NM_080604	Homo sapiens tight junction associated protein 1 (peripheral) (TJAP1), mRNA [NM_080604]	chr6		GO:0005923(tight junction)	GO:0005515(protein binding)
A_23_P24716	NM_017870	TMEM132A	NM_017870	Homo sapiens transmembrane protein 132A (TMEM132A), transcript variant 1, mRNA [NM_017870]	chr11		GO:0016021(integral to membrane)	
A_23_P370682	NM_138456	BATF2	NM_138456	Homo sapiens basic leucine zipper transcription factor, ATF-like 2 (BATF2), mRNA [NM_138456]	chr11	GO:0006355(regulation of transcription, DNA-dependent)	GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0046983(protein dimerization activity)
A_23_P218928	NM_016613	C4orf18	NM_016613	Homo sapiens chromosome 4 open reading frame 18 (C4orf18), transcript variant 2, mRNA [NM_016613]	chr4		GO:0005794(Golgi apparatus)	
A_23_P37560	NM_003847	PEX11A	NM_003847	Homo sapiens peroxisomal biogenesis factor 11A (PEX11A), mRNA [NM_003847]	chr15	GO:0007165(signal transduction);GO:0016559(peroxisome fission)	GO:0005777(peroxisome);GO:0005778(peroxisomal membrane);GO:0005779(integral to peroxisomal membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	
A_23_P120883	NM_002133	HMOX1	NM_002133	Homo sapiens heme oxygenase (decycling) 1 (HMOX1), mRNA [NM_002133]	chr22	GO:0006788(heme oxidation);GO:0043123(positive regulation of I-kappaB kinase/NF-kappaB cascade)	GO:0005624(membrane fraction);GO:0005783(endoplasmic reticulum);GO:0005792(microsome)	GO:0004392(heme oxygenase (decyclizing) activity);GO:0004871(signal transducer activity);GO:0005506(iron ion binding);GO:0016491(oxidoreductase activity);GO:0046872(metal ion binding)
A_24_P271527	NM_014876	JOSD1	NM_014876	Homo sapiens Josephin domain containing 1 (JOSD1), mRNA [NM_014876]	chr22			
A_23_P164047	NM_012329	MMD	NM_012329	Homo sapiens monocyte to macrophage differentiation-associated (MMD), mRNA [NM_012329]	chr17	GO:0019835(cytolysis)	GO:0005624(membrane fraction);GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0004872(receptor activity)
A_24_P149124	NM_004772	C5orf13	NM_004772	Homo sapiens chromosome 5 open reading frame 13 (C5orf13), mRNA [NM_004772]	chr5	GO:0017015(regulation of transforming growth factor beta receptor signaling pathway)		GO:0005515(protein binding)
A_23_P127484	NM_018219	CCDC87	NM_018219	Homo sapiens coiled-coil domain containing 87 (CCDC87), mRNA [NM_018219]	chr11			
A_23_P395438	NM_053044	HTRA3	NM_053044	Homo sapiens HtrA serine peptidase 3 (HTRA3), mRNA [NM_053044]	chr4	GO:0001558(regulation of cell growth);GO:0006508(proteolysis)	GO:0005576(extracellular region)	GO:0004252(serine-type endopeptidase activity);GO:0005515(protein binding);GO:0005520(insulin-like growth factor binding);GO:0008233(peptidase activity)
A_23_P129903	NM_006470	TRIM16	NM_006470	Homo sapiens tripartite motif-containing 16 (TRIM16), mRNA [NM_006470]	chr17		GO:0005622(intracellular);GO:0005737(cytoplasm)	GO:0003700(transcription factor activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P73632	NM_000475	NR0B1	NM_000475	Homo sapiens nuclear receptor subfamily 0, group B, member 1 (NR0B1), mRNA [NM_000475]	chrX	GO:0006350(transcription);GO:0006694(steroid biosynthetic process);GO:0007530(sex determination);GO:0008406(gonad development);GO:0030325(adrenal gland development);GO:0045892(negative regulation of transcription, DNA-dependent)	GO:0005624(membrane fraction);GO:0005634(nucleus);GO:0042788(polysomal ribosome)	GO:0003700(transcription factor activity);GO:0003706(ligand-regulated transcription factor activity);GO:0003707(steroid hormone receptor activity);GO:0003723(RNA binding);GO:0005515(protein binding);GO:0017163(negative regulator of basal transcription activity)
A_24_P110201	A_24_P110201	A_24_P110201			chr4			
A_24_P46093	NM_003043	SLC6A6	NM_003043	Homo sapiens solute carrier family 6 (neurotransmitter transporter, taurine), member 6 (SLC6A6), mRNA [NM_003043]	chr3	GO:0001762(beta-alanine transport);GO:0006520(amino acid metabolic process);GO:0006836(neurotransmitter transport);GO:0015734(taurine transport)	GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0001761(beta-alanine transporter activity);GO:0005369(taurine:sodium symporter activity);GO:0015293(symporter activity)
A_24_P186664	A_24_P186664	A_24_P186664			chr1			
A_24_P240166	NM_145753	PHLDB2	NM_145753	Homo sapiens pleckstrin homology-like domain, family B, member 2 (PHLDB2), mRNA [NM_145753]	chr3			
A_23_P500421	NM_172113	EYA2	NM_172113	Homo sapiens eyes absent homolog 2 (Drosophila) (EYA2), transcript variant 2, mRNA [NM_172113]	chr20	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0007275(multicellular organismal development);GO:0007501(mesodermal cell fate specification);GO:0008152(metabolic process)	GO:0005634(nucleus)	GO:0000287(magnesium ion binding);GO:0003824(catalytic activity);GO:0004721(phosphoprotein phosphatase activity);GO:0004725(protein tyrosine phosphatase activity);GO:0016787(hydrolase activity)
A_23_P18082	NM_032806	C3orf39	NM_032806	Homo sapiens chromosome 3 open reading frame 39 (C3orf39), mRNA [NM_032806]	chr3			GO:0016740(transferase activity)
A_24_P170983	NM_194312	ESPNL	NM_194312	Homo sapiens espin-like (ESPNL), mRNA [NM_194312]	chr2			
A_23_P121898	NM_024615	PARP8	NM_024615	Homo sapiens poly (ADP-ribose) polymerase family, member 8 (PARP8), mRNA [NM_024615]	chr5	GO:0006471(protein amino acid ADP-ribosylation)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003950(NAD+ ADP-ribosyltransferase activity);GO:0016757(transferase activity, transferring glycosyl groups)
A_24_P310616	NM_001032289	SLC35A2	NM_001032289	Homo sapiens solute carrier family 35 (UDP-galactose transporter), member A2 (SLC35A2), transcript variant 2, mRNA [NM_001032289]	chrX	GO:0006012(galactose metabolic process);GO:0008643(carbohydrate transport);GO:0015780(nucleotide-sugar transport);GO:0015785(UDP-galactose transport)	GO:0000139(Golgi membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005338(nucleotide-sugar transporter activity);GO:0005351(sugar porter activity);GO:0005459(UDP-galactose transporter activity)
A_32_P99690	ENST00000380985	NLN		Neurolysin, mitochondrial precursor (EC 3.4.24.16) (Neurotensin endopeptidase) (Mitochondrial oligopeptidase M) (Microsomal endopeptidase) (MEP). [Source:Uniprot/SWISSPROT;Acc:Q9BYT8] [ENST00000380985]	chr5	GO:0006508(proteolysis)	GO:0005739(mitochondrion)	GO:0004222(metalloendopeptidase activity);GO:0008270(zinc ion binding);GO:0016787(hydrolase activity);GO:0046872(metal ion binding)

A_23_P58328	NM_007193	ANXA10	NM_007193	Homo sapiens annexin A10 (ANXA10), mRNA [NM_007193]	chr4		GO:0005739(mitochondrion)	GO:0005509(calcium ion binding);GO:0005544(calcium-dependent phospholipid binding)
A_23_P143120	NM_003183	ADAM17	NM_003183	Homo sapiens ADAM metallopeptidase domain 17 (tumor necrosis factor, alpha, converting enzyme) (ADAM17), mRNA [NM_003183]	chr2	GO:0006508(proteolysis);GO:0007219(Notch signaling pathway);GO:0007267(cell-cell signaling)	GO:0005737(cytoplasm);GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0004222(metalloendopeptidase activity);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P322845	BC033025	PPAPDC1B	BC033025	Homo sapiens phosphatidic acid phosphatase type 2 domain containing 1B, mRNA (cDNA clone MGC:32924 IMAGE:5267610), complete cds. [BC033025]	chr8			
A_23_P215956	NM_002467	MYC	NM_002467	Homo sapiens v-myc myelocytomatosis viral oncogene homolog (avian) (MYC), mRNA [NM_002467]	chr8	GO:0001836(release of cytochrome c from mitochondria);GO:0006309(DNA fragmentation during apoptosis);GO:0006355(regulation of transcription, DNA-dependent);GO:0006357(regulation of transcription from RNA polymerase II promoter);GO:0006879(iron ion homeostasis);GO:0006919(caspase activation);GO:0007050(cell cycle arrest);GO:0008284(positive regulation of cell proliferation);GO:0008629(induction of apoptosis by intracellular signals);GO:0008633(activation of pro-apoptotic gene products);GO:0008634(negative regulation of survival gene product activity);GO:0009314(response to radiation);GO:0042981(regulation of apoptosis)	GO:0005634(nucleus);GO:0005819(spindle)	GO:0003677(DNA binding);GO:0003700(transcription factor activity);GO:0005515(protein binding)
A_23_P15450	NM_018286	TMEM100	NM_018286	Homo sapiens transmembrane protein 100 (TMEM100), mRNA [NM_018286]	chr17		GO:0016020(membrane);GO:0016021(integral to membrane)	
A_24_P305678	NM_012399	PITPNB	NM_012399	Homo sapiens phosphatidylinositol transfer protein, beta (PITPNB), mRNA [NM_012399]	chr22	GO:0006629(lipid metabolic process);GO:0006810(transport)	GO:0005622(intracellular)	GO:0008289(lipid binding);GO:0008526(phosphatidylinositol transporter activity)
A_23_P502142	NM_002037	FYN	NM_002037	Homo sapiens FYN oncogene related to SRC, FGR, YES (FYN), transcript variant 1, mRNA [NM_002037]	chr6	GO:0006468(protein amino acid phosphorylation);GO:0007242(intracellular signaling cascade);GO:0007243(protein kinase cascade);GO:0007275(multicellular organismal development);GO:0007612(learning);GO:0007631(feeding behavior);GO:0050852(T cell receptor signaling pathway)		GO:0000166(nucleotide binding);GO:0004713(protein-tyrosine kinase activity);GO:0005524(ATP binding);GO:0016740(transferase activity);GO:0030145(manganese ion binding);GO:0042802(identical protein binding);GO:0046872(metal ion binding)
A_23_P36658	NM_145791	MGST1	NM_145791	Homo sapiens microsomal glutathione S-transferase 1 (MGST1), transcript variant 1c, mRNA [NM_145791]	chr12	GO:0006749(glutathione metabolic process)	GO:0005739(mitochondrion);GO:0005743(mitochondrial inner membrane);GO:0005783(endoplasmic reticulum);GO:0005792(microsome);GO:0016020(membrane)	GO:0004364(glutathione transferase activity);GO:0016740(transferase activity)
A_23_P352879	M90656	GCLC	M90656	Human gamma-glutamylcysteine synthetase (GCS) mRNA, complete cds. [M90656]	chr6	GO:0006534(cysteine metabolic process);GO:0006536(glutamate metabolic process);GO:0006750(glutathione biosynthetic process);GO:0006916(anti-apoptosis);GO:0006979(response to oxidative stress);GO:0009408(response to heat);GO:0009725(response to hormone stimulus);GO:0016481(negative regulation of transcription);GO:0019852(L-ascorbic acid metabolic process);GO:0030503(regulation of cell redox homeostasis);GO:0050880(regulation of blood vessel size)	GO:0005829(cytosol);GO:0017109(glutamate-cysteine ligase complex)	GO:0000287(magnesium ion binding);GO:0004357(glutamate-cysteine ligase activity);GO:0016595(glutamate binding);GO:0016874(ligase activity);GO:0046982(protein heterodimerization activity);GO:0050662(coenzyme binding)
A_32_P151875	NM_020781	ZNF398	NM_020781	Homo sapiens zinc finger protein 398 (ZNF398), transcript variant 2, mRNA [NM_020781]	chr7	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0008270(zinc ion binding);GO:0016563(transcriptional activator activity);GO:0046872(metal ion binding)
A_24_P258955	NM_020933	ZNF317	NM_020933	Homo sapiens zinc finger protein 317 (ZNF317), mRNA [NM_020933]	chr19	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_24_P759477	NM_002214	ITGB8	NM_002214	Homo sapiens integrin, beta 8 (ITGB8), mRNA [NM_002214]	chr7	GO:0001573(ganglioside metabolic process);GO:0007155(cell adhesion);GO:0007160(cell-matrix adhesion);GO:0007229(integrin-mediated signaling pathway);GO:0007275(multicellular organismal development)	GO:0008305(integrin complex);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0004872(receptor activity);GO:0005515(protein binding)
A_23_P58117	NM_020859	SHROOM3	NM_020859	Homo sapiens shroom family member 3 (SHROOM3), mRNA [NM_020859]	chr4	GO:0000902(cell morphogenesis);GO:0007389(pattern specification process);GO:0045176(apical protein localization)	GO:0005856(cytoskeleton);GO:0005912(adherens junction);GO:0016324(apical plasma membrane)	GO:0003779(actin binding)
A_32_P31618	BC035691	GSR	BC035691	Homo sapiens, clone IMAGE:5756011, mRNA. [BC035691]	chr8	GO:0006118(electron transport);GO:0006749(glutathione metabolic process);GO:0045454(cell redox homeostasis)	GO:0005737(cytoplasm);GO:0005739(mitochondrion)	GO:0004362(glutathione-disulfide reductase activity);GO:0050660(FAD binding);GO:0050661(NADP binding)
A_24_P227831	NM_019862	ABCC1	NM_019862	Homo sapiens ATP-binding cassette, sub-family C (CFTR/MRP), member 1 (ABCC1), transcript variant 2, mRNA [NM_019862]	chr16	GO:0006810(transport);GO:0042493(response to drug)	GO:0005624(membrane fraction);GO:0005887(integral to plasma membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0000166(nucleotide binding);GO:0005215(transporter activity);GO:0005524(ATP binding);GO:0016301(kinase activity);GO:0016740(transferase activity);GO:0016887(ATPase activity);GO:0042626(ATPase activity, coupled to transmembrane movement of substances)

A_23_P14515	NM_152331	ACOT4	NM_152331	Homo sapiens acyl-CoA thioesterase 4 (ACOT4), mRNA [NM_152331]	chr14	GO:0000038(very-long-chain fatty acid metabolic process);GO:0001676(long-chain fatty acid metabolic process);GO:0006104(succinyl-CoA metabolic process);GO:0006629(lipid metabolic process);GO:0006637(acyl-CoA metabolic process);GO:0046459(short-chain fatty acid metabolic process)	GO:0005777(peroxisome)	GO:0004759(serine esterase activity);GO:0016290(palmitoyl-CoA hydrolase activity);GO:0016787(hydrolase activity)
A_23_P204511	NM_017842	FLJ20489	NM_017842	Homo sapiens hypothetical protein FLJ20489 (FLJ20489), mRNA [NM_017842]	chr12			
A_23_P211561	NM_152513	RP5-821D11.2	NM_152513	Homo sapiens meiosis defective 1 (MEI1), mRNA [NM_152513]	chr22			
A_23_P257971	NM_001353	AKR1C1	NM_001353	Homo sapiens aldo-keto reductase family 1, member C1 (dihydrodiol dehydrogenase 1; 20-alpha (3-alpha)-hydroxysteroid dehydrogenase) (AKR1C1), mRNA [NM_001353]	chr10	GO:0006118(electron transport);GO:0006805(xenobiotic metabolic process);GO:0007586(digestion);GO:0008206(bile acid metabolic process);GO:0015721(bile acid and bile salt transport);GO:0030299(cholesterol absorption);GO:0042632(cholesterol homeostasis);GO:0051260(protein homooligomerization)	GO:0005829(cytosol)	GO:0004033(aldo-keto reductase activity);GO:0016491(oxidoreductase activity);GO:0047006(20-alpha-hydroxysteroid dehydrogenase activity);GO:0047042(3-alpha-hydroxysteroid dehydrogenase (B-specific) activity);GO:0047115(trans-1,2-dihydrobenzene-1,2-diol dehydrogenase activity)
A_32_P399546	AF256215	ARNTL2	AF256215	Homo sapiens cycle-like factor CLIF mRNA, complete cds. [AF256215]	chr12	GO:0006355(regulation of transcription, DNA-dependent);GO:0007165(signal transduction);GO:0048511(rhythmic process)	GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0004871(signal transducer activity);GO:0030528(transcription regulator activity)
A_23_P323272	NM_145260	OSR1	NM_145260	Homo sapiens odd-skipped related 1 (Drosophila) (OSR1), mRNA [NM_145260]	chr2	GO:0001656(metanephros development);GO:0007507(heart development);GO:0008406(gonad development);GO:0048389(intermediate mesoderm development)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003676(nucleic acid binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P52589	NM_003475	RASSF7	NM_003475	Homo sapiens Ras association (RalGDS/AF-6) domain family 7 (RASSF7), mRNA [NM_003475]	chr11	GO:0006355(regulation of transcription, DNA-dependent);GO:0007165(signal transduction)	GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0005515(protein binding)
A_24_P281683	XR_018569	LOC441623	XR_018569	PREDICTED: Homo sapiens hypothetical LOC441623 (LOC441623), mRNA [XR_018569]	chr11			
A_24_P171983	NM_014165	C6orf66	NM_014165	Homo sapiens chromosome 6 open reading frame 66 (C6orf66), mRNA [NM_014165]	chr6			
A_24_P584992	BU732811	BU732811	BU732811	UI-E-CQ1-afz-j-16-0-UI.s1 UI-E-CQ1 Homo sapiens cDNA clone UI-E-CQ1-afz-j-16-0-UI 3', mRNA sequence [BU732811]	chr12			
A_24_P183150	NM_002090	CXCL3	NM_002090	Homo sapiens chemokine (C-X-C motif) ligand 3 (CXCL3), mRNA [NM_002090]	chr4	GO:0006935(chemotaxis);GO:0006954(inflammatory response);GO:0006955(immune response);GO:0007186(G-protein coupled receptor protein signaling pathway)	GO:0005576(extracellular region);GO:0005615(extracellular space)	GO:0008009(chemokine activity)
A_23_P57760	NM_152282	ACPL2	NM_152282	Homo sapiens acid phosphatase-like 2 (ACPL2), transcript variant 1, mRNA [NM_152282]	chr3			GO:0003993(acid phosphatase activity)
A_24_P919330	NM_002032	FTH1	NM_002032	Homo sapiens ferritin, heavy polypeptide 1 (FTH1), mRNA [NM_002032]	chr11	GO:0006826(iron ion transport);GO:0006879(iron ion homeostasis);GO:0006880(intracellular sequestering of iron ion);GO:0006955(immune response);GO:0008283(cell proliferation);GO:0008285(negative regulation of cell proliferation)	GO:0005886(plasma membrane);GO:0008043(ferritin complex)	GO:0004322(ferroxidase activity);GO:0005488(binding);GO:0005515(protein binding);GO:0008199(ferric iron binding);GO:0016491(oxidoreductase activity);GO:0019900(kinase binding)
A_23_P140405	NM_005197	FOXN3	NM_005197	Homo sapiens checkpoint suppressor 1 (CHES1), mRNA [NM_005197]	chr14	GO:0000077(DNA damage checkpoint);GO:0000085(G2 phase of mitotic cell cycle);GO:0006350(transcription);GO:0007049(cell cycle);GO:0045892(negative regulation of transcription, DNA-dependent)	GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0005515(protein binding);GO:0016564(transcriptional repressor activity)
A_23_P9894	NM_005788	PRMT3	NM_005788	Homo sapiens protein arginine methyltransferase 3 (PRMT3), mRNA [NM_005788]	chr11	GO:0008152(metabolic process)	GO:0005622(intracellular);GO:0005737(cytoplasm)	GO:0003676(nucleic acid binding);GO:0008168(methyltransferase activity);GO:0008270(zinc ion binding);GO:0016274(protein-arginine N-methyltransferase activity);GO:0016740(transferase activity);GO:0046872(metal ion binding)
A_23_P89798	NM_001012515	FECH	NM_001012515	Homo sapiens ferrochelatase (protoporphyria) (FECH), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA [NM_001012515]	chr18	GO:0006091(generation of precursor metabolites and energy);GO:0006783(heme biosynthetic process);GO:0009416(response to light stimulus);GO:0009589(detection of UV)	GO:0005739(mitochondrion)	GO:0004325(ferrochelatase activity);GO:0008198(ferrous iron binding);GO:0046872(metal ion binding)
A_24_P347447	NM_014992	DAAM1	NM_014992	Homo sapiens dishevelled associated activator of morphogenesis 1 (DAAM1), mRNA [NM_014992]	chr14	GO:0016043(cellular component organization and biogenesis);GO:0030036(actin cytoskeleton organization and biogenesis)		GO:0003779(actin binding);GO:0017048(Rho GTPase binding)

A_23_P411296	NM_005194	CEBPB	NM_005194	Homo sapiens CCAAT/enhancer binding protein (C/EBP), beta (CEBPB), mRNA [NM_005194]	chr20	GO:0001892(embryonic placenta development);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006366(transcription from RNA polymerase II promoter);GO:0006916(anti-apoptosis);GO:0006917(induction of apoptosis);GO:0006953(acute-phase response);GO:0006954(inflammatory response);GO:0006955(immune response);GO:0030182(neuron differentiation);GO:0045408(regulation of interleukin-6 biosynthetic process);GO:0045444(fat cell differentiation);GO:0045941(positive regulation of transcription)	GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0003700(transcription factor activity);GO:0016563(transcriptional activator activity);GO:0042803(protein homodimerization activity);GO:0046982(protein heterodimerization activity)
A_23_P309361	NM_144584	C1orf59	NM_144584	Homo sapiens chromosome 1 open reading frame 59 (C1orf59), mRNA [NM_144584]	chr1			
A_23_P113793	NM_024508	ZBED2	NM_024508	Homo sapiens zinc finger, BED-type containing 2 (ZBED2), mRNA [NM_024508]	chr3			GO:0003677(DNA binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P88865	NM_144601	CMTM3	NM_144601	Homo sapiens CKLF-like MARVEL transmembrane domain containing 3 (CMTM3), transcript variant 1, mRNA [NM_144601]	chr16	GO:0006935(chemotaxis)	GO:0005615(extracellular space);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005125(cytokine activity)
A_23_P33326	NM_000679	ADRA1B	NM_000679	Homo sapiens adrenergic, alpha-1B-, receptor (ADRA1B), mRNA [NM_000679]	chr5	GO:0007165(signal transduction);GO:0007186(G-protein coupled receptor protein signaling pathway);GO:0007188(G-protein signaling, coupled to cAMP nucleotide second messenger);GO:0007243(protein kinase cascade);GO:0007267(cell-cell signaling);GO:0007275(multicellular organismal development);GO:0007512(adult heart development);GO:0007626(locomotory behavior);GO:0008283(cell proliferation);GO:0008542(visual learning);GO:0016049(cell growth);GO:0035265(organ growth);GO:0042593(glucose homeostasis);GO:0043278(response to morphine);GO:0045818(negative regulation of glycogen catabolic process);GO:0045819(positive regulation of glycogen catabolic process);GO:0048148(behavioral response to cocaine)	GO:0000299(integral to membrane of membrane fraction);GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0001584(rhodopsin-like receptor activity);GO:0004872(receptor activity);GO:0004935(adrenoceptor activity);GO:0004937(alpha1-adrenergic receptor activity)
A_23_P128744	NM_000710	BDKRB1	NM_000710	Homo sapiens bradykinin receptor B1 (BDKRB1), mRNA [NM_000710]	chr14	GO:0006954(inflammatory response);GO:0007165(signal transduction);GO:0007186(G-protein coupled receptor protein signaling pathway);GO:0007204(elevation of cytosolic calcium ion concentration)	GO:0005783(endoplasmic reticulum);GO:0005886(plasma membrane);GO:0005887(integral to plasma membrane)	GO:0001584(rhodopsin-like receptor activity);GO:0004872(receptor activity);GO:0004947(bradykinin receptor activity)
A_24_P126060	NM_001356	DDX3X	NM_001356	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 3, X-linked (DDX3X), mRNA [NM_001356]	chrX		GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0000166(nucleotide binding);GO:0003677(DNA binding);GO:0003723(RNA binding);GO:0004004(ATP-dependent RNA helicase activity);GO:0005524(ATP binding);GO:0016787(hydrolase activity)
A_23_P23346	NM_006818	MLLT11	NM_006818	Homo sapiens myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 11 (MLLT11), mRNA [NM_006818]	chr1		GO:0005575(cellular_component)	GO:0003674(molecular_function)
A_23_P84448	NM_006000	TUBA4A	NM_006000	Homo sapiens tubulin, alpha 4a (TUBA4A), mRNA [NM_006000]	chr2	GO:0007018(microtubule-based movement);GO:0051258(protein polymerization)	GO:0005874(microtubule);GO:0043234(protein complex)	GO:0000166(nucleotide binding);GO:0003924(GTPase activity);GO:0005198(structural molecule activity);GO:0005515(protein binding);GO:0005525(GTP binding)
A_23_P44724	NM_001321	CSRP2	NM_001321	Homo sapiens cysteine and glycine-rich protein 2 (CSRP2), mRNA [NM_001321]	chr12	GO:0007275(multicellular organismal development);GO:0007517(muscle development);GO:0008283(cell proliferation);GO:0009887(organ morphogenesis);GO:0016049(cell growth);GO:0030154(cell differentiation)	GO:0005634(nucleus)	GO:0003674(molecular_function);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P112241	NM_012266	DNAJB5	NM_012266	Homo sapiens DnaJ (Hsp40) homolog, subfamily B, member 5 (DNAJB5), mRNA [NM_012266]	chr9	GO:0006457(protein folding);GO:0006986(response to unfolded protein)		GO:0031072(heat shock protein binding);GO:0051082(unfolded protein binding)
A_23_P23669	NM_017734	PALMD	NM_017734	Homo sapiens palmdelphin (PALMD), mRNA [NM_017734]	chr1	GO:0008360(regulation of cell shape)	GO:0016020(membrane)	
A_23_P372834	NM_198098	AQP1	NM_198098	Homo sapiens aquaporin 1 (Colton blood group) (AQP1), mRNA [NM_198098]	chr7	GO:0006810(transport);GO:0006833(water transport);GO:0007588(excretion)	GO:0005887(integral to plasma membrane);GO:0016020(membrane);GO:0016021(integral to membrane);GO:0019867(outer membrane)	GO:0005215(transporter activity);GO:0005372(water transporter activity);GO:0015288(porin activity)
A_23_P119923	NM_020184	CNNM4	NM_020184	Homo sapiens cyclin M4 (CNNM4), mRNA [NM_020184]	chr2			
A_32_P204169	ENST00000370703	TTLL7		Tubulin--tyrosine ligase-like protein 7 (Testis development protein NYD-SP30). [Source:Uniprot/SWISSPROT;Acc:Q6ZT98] [ENST00000370703]	chr1	GO:0006464(protein modification process)		GO:0004835(tubulin-tyrosine ligase activity);GO:0016874(ligase activity)

A_23_P114947	NM_002923	RGS2	NM_002923	Homo sapiens regulator of G-protein signalling 2, 24kDa (RGS2), mRNA [NM_002923]	chr1	GO:0007049(cell cycle);GO:0007169(transmembrane receptor protein tyrosine kinase signaling pathway);GO:0008277(regulation of G-protein coupled receptor protein signaling pathway);GO:0009968(negative regulation of signal transduction)		GO:0004871(signal transducer activity);GO:0005096(GTPase activator activity);GO:0005516(calmodulin binding)
A_23_P202071	NM_006561	CUGBP2	NM_006561	Homo sapiens CUG triplet repeat, RNA binding protein 2 (CUGBP2), transcript variant 2, mRNA [NM_006561]	chr10	GO:0006396(RNA processing);GO:0007528(neuromuscular junction development);GO:0008016(regulation of heart contraction)		GO:0000166(nucleotide binding);GO:0003723(RNA binding)
A_24_P296808	NM_018215	FLJ10781	NM_018215	Homo sapiens hypothetical protein FLJ10781 (FLJ10781), mRNA [NM_018215]	chr19			
A_23_P352402	NM_153256	C10orf47	NM_153256	Homo sapiens chromosome 10 open reading frame 47 (C10orf47), mRNA [NM_153256]	chr10			
A_24_P29401	NM_181523	PIK3R1	NM_181523	Homo sapiens phosphoinositide-3-kinase, regulatory subunit 1 (p85 alpha) (PIK3R1), transcript variant 1, mRNA [NM_181523]	chr5	GO:0006955(immune response);GO:0007242(intracellular signaling cascade);GO:0008286(insulin receptor signaling pathway);GO:0046854(phosphoinositide phosphorylation);GO:0048009(insulin-like growth factor receptor signaling pathway)	GO:0005622(intracellular);GO:0035030(phosphoinositide 3-kinase complex, class IA)	GO:0003924(GTPase activity);GO:0005158(insulin receptor binding);GO:0005159(insulin-like growth factor receptor binding);GO:0005525(GTP binding);GO:0005545(phosphatidylinositol binding);GO:0019903(protein phosphatase binding);GO:0035014(phosphoinositide 3-kinase regulator activity);GO:0043125(ErbB-3 class receptor binding)
A_24_P945283	NM_021120	DLG3	NM_021120	Homo sapiens discs, large homolog 3 (neuroendocrine-dlg, Drosophila) (DLG3), transcript variant 1, mRNA [NM_021120]	chrX	GO:0008285(negative regulation of cell proliferation)	GO:0005575(cellular_component)	GO:0004385(guanylate kinase activity);GO:0005515(protein binding)
A_23_P320113	NM_080725	SRXN1	NM_080725	Homo sapiens sulfiredoxin 1 homolog (S. cerevisiae) (SRXN1), mRNA [NM_080725]	chr20	GO:0006979(response to oxidative stress)	GO:0005829(cytosol)	GO:0000166(nucleotide binding);GO:0000287(magnesium ion binding);GO:0005524(ATP binding);GO:0016209(antioxidant activity);GO:0016667(oxidoreductase activity, acting on sulfur group of donors)
A_23_P325690	NM_144698	ANKRD35	NM_144698	Homo sapiens ankyrin repeat domain 35 (ANKRD35), mRNA [NM_144698]	chr1			
A_23_P121716	NM_005139	ANXA3	NM_005139	Homo sapiens annexin A3 (ANXA3), mRNA [NM_005139]	chr4	GO:0007165(signal transduction)	GO:0005737(cytoplasm)	GO:0005509(calcium ion binding);GO:0005544(calcium-dependent phospholipid binding);GO:0008486(diphosphoinositol-polyphosphate diphosphatase activity);GO:0019834(phospholipase A2 inhibitor activity)
A_23_P86100	NM_001007255	KARCA1	NM_001007255	Homo sapiens kelch/ankyrin repeat containing cyclin A1 interacting protein (KARCA1), transcript variant 2, mRNA [NM_001007255]	chr1			
A_23_P48585	NM_005407	SALL2	NM_005407	Homo sapiens sal-like 2 (Drosophila) (SALL2), mRNA [NM_005407]	chr14	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P73097	NM_170587	RGS20	NM_170587	Homo sapiens regulator of G-protein signalling 20 (RGS20), transcript variant 1, mRNA [NM_170587]	chr8	GO:0008277(regulation of G-protein coupled receptor protein signaling pathway);GO:0009968(negative regulation of signal transduction)	GO:0016020(membrane)	GO:0004871(signal transducer activity);GO:0005096(GTPase activator activity);GO:0005515(protein binding)
A_24_P902653	BM997931	BM997931	BM997931	UI-H-DI0-auw-m-10-0-UI.s1 NCI_CGAP_DI0 Homo sapiens cDNA clone IMAGE:5875377 3', mRNA sequence [BM997931]	chr19			
A_23_P81399	NM_003900	SQSTM1	NM_003900	Homo sapiens sequestosome 1 (SQSTM1), mRNA [NM_003900]	chr5	GO:0006511(ubiquitin-dependent protein catabolic process);GO:0006915(apoptosis);GO:0006950(response to stress);GO:0006955(immune response);GO:0007242(intracellular signaling cascade);GO:0008104(protein localization);GO:0016197(endosome transport);GO:0030154(cell differentiation);GO:0043122(regulation of I-kappaB kinase/NF-kappaB cascade);GO:0045944(positive regulation of transcription from RNA polymerase II promoter)	GO:0005634(nucleus);GO:0005829(cytosol)	GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0019901(protein kinase binding);GO:0030971(receptor tyrosine kinase binding);GO:0042169(SH2 domain binding);GO:0043130(ubiquitin binding);GO:0046872(metal ion binding)
A_32_P99097	NM_002270	TNPO1	NM_002270	Homo sapiens transportin 1 (TNPO1), transcript variant 1, mRNA [NM_002270]	chr5	GO:0000059(protein import into nucleus, docking);GO:0000060(protein import into nucleus, translocation);GO:0006886(intracellular protein transport)	GO:0005634(nucleus);GO:0005643(nuclear pore);GO:0005737(cytoplasm)	GO:0005515(protein binding);GO:0008139(nuclear localization sequence binding);GO:0008565(protein transporter activity)
A_24_P944383	AL050107	WWTR1	AL050107	Homo sapiens mRNA; cDNA DKFZp586I1419 (from clone DKFZp586I1419); partial cds. [AL050107]	chr3	GO:0000122(negative regulation of transcription from RNA polymerase II promoter);GO:0001649(osteoblast differentiation);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0045599(negative regulation of fat cell differentiation);GO:0045944(positive regulation of transcription from RNA polymerase II promoter)	GO:0005634(nucleus);GO:0005667(transcription factor complex);GO:0005737(cytoplasm)	GO:0003713(transcription coactivator activity);GO:0003714(transcription corepressor activity);GO:0005515(protein binding);GO:0030528(transcription regulator activity)

A_23_P41344	NM_001432	EREG	NM_001432	Homo sapiens epiregulin (EREG), mRNA [NM_001432]	chr4	GO:0000074(regulation of progression through cell cycle);GO:0001525(angiogenesis);GO:0001550(ovarian cumulus expansion);GO:0001556(oocyte maturation);GO:0001819(positive regulation of cytokine production);GO:0007143(female meiosis);GO:0007173(epidermal growth factor receptor signaling pathway);GO:0007267(cell-cell signaling);GO:0007275(multicellular organismal development);GO:0009299(mRNA transcription);GO:0009887(organ morphogenesis);GO:0016481(negative regulation of transcription);GO:0019221(cytokine and chemokine mediated signaling pathway);GO:0030216(keratinocyte differentiation);GO:0030728(ovulation);GO:0042060(wound healing);GO:0042327(positive regulation of phosphorylation);GO:0042700(luteinizing hormone signaling pathway);GO:0045089(positive regulation of innate immune response);GO:0045410(positive regulation of interleukin-6 biosynthetic process);GO:0045740(positive regulation of DNA replication);GO:0045741(positive regulation of epidermal growth factor receptor activity);GO:0045766(positive regulation of angiogenesis);GO:0045840(positive regulation of mitosis);GO:0045860(positive regulation of protein kinase activity);GO:0048146(positive regulation of fibroblast proliferation);GO:0048160(primary follicle stage oogenesis	GO:0005615(extracellular space);GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0005154(epidermal growth factor receptor binding);GO:0005515(protein binding);GO:0008083(growth factor activity);GO:0046982(protein heterodimerization activity)
A_24_P220947	NM_001353	AKR1C1	NM_001353	Homo sapiens aldo-keto reductase family 1, member C1 (dihydrodiol dehydrogenase 1; 20-alpha (3-alpha)-hydroxysteroid dehydrogenase) (AKR1C1), mRNA [NM_001353]	chr10	GO:0006118(electron transport);GO:0006805(xenobiotic metabolic process);GO:0007586(digestion);GO:0008206(bile acid metabolic process);GO:0015721(bile acid and bile salt transport);GO:0030299(cholesterol absorption);GO:0042632(cholesterol homeostasis);GO:0051260(protein homooligomerization)	GO:0005829(cytosol)	GO:0004033(aldo-keto reductase activity);GO:0016491(oxidoreductase activity);GO:0047006(20-alpha-hydroxysteroid dehydrogenase activity);GO:0047042(3-alpha-hydroxysteroid dehydrogenase (B-specific) activity);GO:0047115(trans-1,2-dihydrobenzene-1,2-diol dehydrogenase activity)
A_32_P132206	NM_017414	USP18	NM_017414	Homo sapiens ubiquitin specific peptidase 18 (USP18), mRNA [NM_017414]	chr22	GO:0006511(ubiquitin-dependent protein catabolic process);GO:0006512(ubiquitin cycle)	GO:0005634(nucleus)	GO:0004221(ubiquitin thiolesterase activity);GO:0008234(cysteine-type peptidase activity)
A_23_P127915	NM_030906	STK33	NM_030906	Homo sapiens serine/threonine kinase 33 (STK33), mRNA [NM_030906]	chr11	GO:0006468(protein amino acid phosphorylation)		GO:0000166(nucleotide binding);GO:0004674(protein serine/threonine kinase activity);GO:0005524(ATP binding);GO:0016740(transferase activity)
A_24_P478940	THC2668815	THC2668815		Q4TBH3_TETNG (Q4TBH3) Chromosome 13 SCAF7124, whole genome shotgun sequence, partial (3%) [THC2668815]	chr9			
A_32_P230720	NM_198256	E2F6	NM_198256	Homo sapiens E2F transcription factor 6 (E2F6), mRNA [NM_198256]	chr2	GO:0000074(regulation of progression through cell cycle);GO:0000122(negative regulation of transcription from RNA polymerase II promoter);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0007049(cell cycle)	GO:0005634(nucleus);GO:0005667(transcription factor complex)	GO:0003700(transcription factor activity);GO:0003714(transcription corepressor activity)
A_23_P38876	NM_005357	LIPE	NM_005357	Homo sapiens lipase, hormone-sensitive (LIPE), mRNA [NM_005357]	chr19	GO:0006091(generation of precursor metabolites and energy);GO:0006468(protein amino acid phosphorylation);GO:0006631(fatty acid metabolic process);GO:0007565(pregnancy);GO:0008202(steroid metabolic process);GO:0008203(cholesterol metabolic process);GO:0016042(lipid catabolic process);GO:0019433(triacylglycerol catabolic process);GO:0042493(response to drug);GO:0046340(diacylglycerol catabolic process)		GO:0005515(protein binding);GO:0016788(hydrolase activity, acting on ester bonds);GO:0047372(acylglycerol lipase activity)
A_23_P256231	NM_032145	FBXO30	NM_032145	Homo sapiens F-box protein 30 (FBXO30), mRNA [NM_032145]	chr6	GO:0006512(ubiquitin cycle)		GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P62901	NM_006763	BTG2	NM_006763	Homo sapiens BTG family, member 2 (BTG2), mRNA [NM_006763]	chr1	GO:0006281(DNA repair);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006479(protein amino acid methylation);GO:0008285(negative regulation of cell proliferation);GO:0009952(anterior/posterior pattern formation)		GO:0003700(transcription factor activity);GO:0005515(protein binding)
A_24_P152968	NM_001353	AKR1C1	NM_001353	Homo sapiens aldo-keto reductase family 1, member C1 (dihydrodiol dehydrogenase 1; 20-alpha (3-alpha)-hydroxysteroid dehydrogenase) (AKR1C1), mRNA [NM_001353]	chr10	GO:0006118(electron transport);GO:0006805(xenobiotic metabolic process);GO:0007586(digestion);GO:0008206(bile acid metabolic process);GO:0015721(bile acid and bile salt transport);GO:0030299(cholesterol absorption);GO:0042632(cholesterol homeostasis);GO:0051260(protein homooligomerization)	GO:0005829(cytosol)	GO:0004033(aldo-keto reductase activity);GO:0016491(oxidoreductase activity);GO:0047006(20-alpha-hydroxysteroid dehydrogenase activity);GO:0047042(3-alpha-hydroxysteroid dehydrogenase (B-specific) activity);GO:0047115(trans-1,2-dihydrobenzene-1,2-diol dehydrogenase activity)
A_23_P35066	NM_015976	SNX7	NM_015976	Homo sapiens sorting nexin 7 (SNX7), transcript variant 1, mRNA [NM_015976]	chr1	GO:0007154(cell communication);GO:0015031(protein transport)		GO:0005515(protein binding);GO:0035091(phosphoinositide binding)
A_23_P157809	NM_012212	LTB4DH	NM_012212	Homo sapiens leukotriene B4 12-hydroxydehydrogenase (LTB4DH), mRNA [NM_012212]	chr9	GO:0006691(leukotriene metabolic process)	GO:0005737(cytoplasm)	GO:0004022(alcohol dehydrogenase activity);GO:0008270(zinc ion binding);GO:0016491(oxidoreductase activity);GO:0047522(15-oxoprostaglandin 13-oxidase activity)

A_23_P385126	NM_139160	DEPDC7	NM_139160	Homo sapiens DEP domain containing 7 (DEPDC7), transcript variant 2, mRNA [NM_139160]	chr11	GO:0007242(intracellular signaling cascade);GO:0008150(biological_process)	GO:0005575(cellular_component)	GO:0003674(molecular_function)
A_24_P659113	NM_152523	CCNYL1	NM_152523	Homo sapiens cyclin Y-like 1 (CCNYL1), mRNA [NM_152523]	chr2	GO:0000074(regulation of progression through cell cycle)		
A_23_P204654	NM_000899	KITLG	NM_000899	Homo sapiens KIT ligand (KITLG), transcript variant b, mRNA [NM_000899]	chr12	GO:0007155(cell adhesion);GO:0007165(signal transduction);GO:0008283(cell proliferation);GO:0009887(organ morphogenesis);GO:0030097(hemopoiesis)	GO:0005886(plasma membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005173(stem cell factor receptor binding);GO:0005515(protein binding);GO:0008083(growth factor activity)
A_24_P503669	AK093628	AK093628	AK093628	Homo sapiens cDNA FLJ36309 fis, clone THYMU2004986. [AK093628]	chr15			
A_23_P77415	NM_013370	OSGIN1	NM_013370	Homo sapiens oxidative stress induced growth inhibitor 1 (OSGIN1), transcript variant 1, mRNA [NM_013370]	chr16	GO:0007275(multicellular organismal development);GO:0030154(cell differentiation);GO:0030308(negative regulation of cell growth)	GO:0005575(cellular_component)	GO:0008083(growth factor activity)
A_24_P129341	NM_020299	AKR1B10	NM_020299	Homo sapiens aldo-keto reductase family 1, member B10 (aldose reductase) (AKR1B10), mRNA [NM_020299]	chr7	GO:0006081(aldehyde metabolic process);GO:0007586(digestion);GO:0008202(steroid metabolic process)	GO:0005575(cellular_component)	GO:0004033(aldo-keto reductase activity);GO:0016491(oxidoreductase activity)
A_23_P106682	NM_001424	EMP2	NM_001424	Homo sapiens epithelial membrane protein 2 (EMP2), mRNA [NM_001424]	chr16	GO:0007275(multicellular organismal development);GO:0008219(cell death);GO:0008283(cell proliferation)	GO:0016020(membrane);GO:0016021(integral to membrane)	
A_24_P197196	NM_005689	ABCB6	NM_005689	Homo sapiens ATP-binding cassette, sub-family B (MDR/TAP), member 6 (ABCB6), nuclear gene encoding mitochondrial protein, mRNA [NM_005689]	chr2	GO:0006810(transport);GO:0006879(iron ion homeostasis)	GO:0005739(mitochondrion);GO:0005740(mitochondrial envelope);GO:0016020(membrane);GO:0016021(integral to membrane);GO:0019867(outer membrane);GO:0043190(ATP-binding cassette (ABC) transporter complex)	GO:0000166(nucleotide binding);GO:0005524(ATP binding);GO:0016887(ATPase activity);GO:0042626(ATPase activity, coupled to transmembrane movement of substances)
A_23_P11543	NM_000147	FUCA1	NM_000147	Homo sapiens fucosidase, alpha-L- 1, tissue (FUCA1), mRNA [NM_000147]	chr1	GO:0005975(carbohydrate metabolic process);GO:0006027(glycosaminoglycan catabolic process);GO:0008152(metabolic process)	GO:0005737(cytoplasm);GO:0005764(lysosome)	GO:0003824(catalytic activity);GO:0004560(alpha-L-fucosidase activity);GO:0016798(hydrolase activity, acting on glycosyl bonds);GO:0043169(cation binding)
A_24_P941649	AL834189	VPS37A	AL834189	Homo sapiens mRNA; cDNA DKFZp762I185 (from clone DKFZp762I185). [AL834189]	chr8			
A_23_P142380	NM_005858	AKAP8	NM_005858	Homo sapiens A kinase (PRKA) anchor protein 8 (AKAP8), mRNA [NM_005858]	chr19	GO:0006810(transport);GO:0007067(mitosis);GO:0007076(mitotic chromosome condensation);GO:0007165(signal transduction)	GO:0000793(condensed chromosome);GO:0001939(female pronucleus);GO:0005622(intracellular);GO:0005634(nucleus);GO:0016020(membrane)	GO:0003677(DNA binding);GO:0005351(sugar porter activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding);GO:0051018(protein kinase A binding)
A_32_P60065	NM_004101	F2RL2	NM_004101	Homo sapiens coagulation factor II (thrombin) receptor-like 2 (F2RL2), mRNA [NM_004101]	chr5	GO:0007165(signal transduction);GO:0007186(G-protein coupled receptor protein signaling pathway);GO:0007596(blood coagulation);GO:0009611(response to wounding)	GO:0005886(plasma membrane);GO:0005887(integral to plasma membrane)	GO:0001584(rhodopsin-like receptor activity);GO:0004435(phosphoinositide phospholipase C activity);GO:0004872(receptor activity);GO:0015057(thrombin receptor activity)
A_23_P417942	NM_001024948	FNBP1L	NM_001024948	Homo sapiens formin binding protein 1-like (FNBP1L), transcript variant 1, mRNA [NM_001024948]	chr1	GO:0006412(translation);GO:0006897(endocytosis)	GO:0005622(intracellular);GO:0005840(ribosome);GO:0005856(cytoskeleton);GO:0016020(membrane)	GO:0003723(RNA binding);GO:0003735(structural constituent of ribosome);GO:0008289(lipid binding);GO:0031072(heat shock protein binding)
A_23_P103232	NM_017823	DUSP23	NM_017823	Homo sapiens dual specificity phosphatase 23 (DUSP23), mRNA [NM_017823]	chr1	GO:0006470(protein amino acid dephosphorylation)	GO:0005634(nucleus)	GO:0004725(protein tyrosine phosphatase activity);GO:0008138(protein tyrosine/serine/threonine phosphatase activity);GO:0016787(hydrolase activity)
A_23_P44993	NM_006755	TALDO1	NM_006755	Homo sapiens transaldolase 1 (TALDO1), mRNA [NM_006755]	chr11	GO:0005975(carbohydrate metabolic process);GO:0006098(pentose-phosphate shunt);GO:0008152(metabolic process)	GO:0005737(cytoplasm)	GO:0003824(catalytic activity);GO:0004801(transaldolase activity);GO:0005515(protein binding);GO:0016740(transferase activity)
A_23_P143713	NM_021822	APOBEC3G	NM_021822	Homo sapiens apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G (APOBEC3G), mRNA [NM_021822]	chr22	GO:0006410(transcription, RNA-dependent);GO:0009615(response to virus);GO:0016553(base conversion or substitution editing);GO:0045087(innate immune response);GO:0045869(negative regulation of retroviral genome replication);GO:0048525(negative regulation of viral life cycle)	GO:0005634(nucleus);GO:0030895(apolipoprotein B mRNA editing enzyme complex)	GO:0003723(RNA binding);GO:0004126(cytidine deaminase activity);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0016787(hydrolase activity);GO:0042803(protein homodimerization activity);GO:0046872(metal ion binding)
A_24_P295245	NM_032467	ASPH	NM_032467	Homo sapiens aspartate beta-hydroxylase (ASPH), transcript variant 4, mRNA [NM_032467]	chr8	GO:0006936(muscle contraction);GO:0008150(biological_process);GO:0018193(peptidyl-amino acid modification)	GO:0005783(endoplasmic reticulum);GO:0005789(endoplasmic reticulum membrane);GO:0016020(membrane);GO:0016021(integral to membrane);GO:0030176(integral to endoplasmic reticulum membrane)	GO:0004597(peptide-aspartate beta-dioxygenase activity);GO:0005488(binding);GO:0005506(iron ion binding);GO:0005509(calcium ion binding);GO:0008307(structural constituent of muscle);GO:0009055(electron carrier activity);GO:0016702(oxidoreductase activity, acting on single donors with incorporation of molecular oxygen, incorporation of two atoms of oxygen)
A_24_P120934	NM_006705	GADD45G	NM_006705	Homo sapiens growth arrest and DNA-damage-inducible, gamma (GADD45G), mRNA [NM_006705]	chr9	GO:0000185(activation of MAPKKK activity);GO:0006281(DNA repair);GO:0006915(apoptosis);GO:0006950(response to stress);GO:0007275(multicellular organismal development);GO:0030154(cell differentiation)		GO:0005515(protein binding)
A_23_P154058	NM_172195	EIF2B4	NM_172195	Homo sapiens eukaryotic translation initiation factor 2B, subunit 4 delta, 67kDa (EIF2B4), transcript variant 1, mRNA [NM_172195]	chr2	GO:0001541(ovarian follicle development);GO:0006413(translational initiation);GO:0006417(regulation of translation);GO:0009408(response to heat);GO:0009749(response to glucose stimulus);GO:0042552(myelination);GO:0043434(response to peptide hormone stimulus);GO:0044237(cellular metabolic process)	GO:0005737(cytoplasm);GO:0005851(eukaryotic translation initiation factor 2B complex)	GO:0003743(translation initiation factor activity);GO:0005085(guanyl-nucleotide exchange factor activity);GO:0005515(protein binding)

A_32_P129621	NM_003183	ADAM17	NM_003183	Homo sapiens ADAM metallopeptidase domain 17 (tumor necrosis factor, alpha, converting enzyme) (ADAM17), mRNA [NM_003183]	chr2	GO:0006508(proteolysis);GO:0007219(Notch signaling pathway);GO:0007267(cell-cell signaling)	GO:0005737(cytoplasm);GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0004222(metalloendopeptidase activity);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P416289	NM_033425	DIXDC1	NM_033425	Homo sapiens DIX domain containing 1 (DIXDC1), transcript variant 2, mRNA [NM_033425]	chr11	GO:0007275(multicellular organismal development)	GO:0005622(intracellular)	GO:0004871(signal transducer activity)
A_23_P85952	NM_024901	DENND2D	NM_024901	Homo sapiens DENN/MADD domain containing 2D (DENND2D), mRNA [NM_024901]	chr1			
A_23_P34093	NM_000402	G6PD	NM_000402	Homo sapiens glucose-6-phosphate dehydrogenase (G6PD), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA [NM_000402]	chrX	GO:0005975(carbohydrate metabolic process);GO:0006006(glucose metabolic process);GO:0006010(glucose 6-phosphate utilization);GO:0006098(pentose-phosphate shunt)	GO:0005575(cellular_component);GO:0005737(cytoplasm)	GO:0004345(glucose-6-phosphate 1-dehydrogenase activity);GO:0016491(oxidoreductase activity)
A_23_P16722	NM_014689	DOCK10	NM_014689	Homo sapiens dedicator of cytokinesis 10 (DOCK10), mRNA [NM_014689]	chr2			GO:0004872(receptor activity);GO:0005085(guanyl-nucleotide exchange factor activity);GO:0005525(GTP binding);GO:0051020(GTPase binding)
A_23_P82169	NM_003107	SOX4	NM_003107	Homo sapiens SRY (sex determining region Y)-box 4 (SOX4), mRNA [NM_003107]	chr6	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0031017(exocrine pancreas development)	GO:0005634(nucleus)	GO:0003700(transcription factor activity)
A_23_P67529	NM_002250	KCNN4	NM_002250	Homo sapiens potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4 (KCNN4), mRNA [NM_002250]	chr19	GO:0006811(ion transport);GO:0006813(potassium ion transport);GO:0006952(defense response);GO:0050714(positive regulation of protein secretion)	GO:0005624(membrane fraction);GO:0008076(voltage-gated potassium channel complex);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005216(ion channel activity);GO:0005249(voltage-gated potassium channel activity);GO:0005516(calmodulin binding);GO:0015269(calcium-activated potassium channel activity)
A_24_P924697	AK055915	AK055915	AK055915	Homo sapiens cDNA FLJ31353 fis, clone MESAN2000264. [AK055915]	chr2			
A_24_P21831	NM_019591	ZNF26	NM_019591	Homo sapiens zinc finger protein 26 (ZNF26), mRNA [NM_019591]	chr12	GO:0006355(regulation of transcription, DNA-dependent)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003676(nucleic acid binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P36266	NM_003477	PDHX	NM_003477	Homo sapiens pyruvate dehydrogenase complex, component X (PDHX), mRNA [NM_003477]	chr11	GO:0008152(metabolic process)	GO:0005739(mitochondrion)	GO:0005515(protein binding);GO:0008415(acyltransferase activity);GO:0031405(lipoic acid binding)
A_23_P329271	NM_002386	MC1R	NM_002386	Homo sapiens melanocortin 1 receptor (alpha melanocyte stimulating hormone receptor) (MC1R), mRNA [NM_002386]	chr16	GO:0007165(signal transduction);GO:0007187(G-protein signaling, coupled to cyclic nucleotide second messenger);GO:0007275(multicellular organismal development);GO:0009650(UV protection)	GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0001584(rhodopsin-like receptor activity);GO:0004872(receptor activity);GO:0004980(melanocyte stimulating hormone receptor activity)
A_24_P274814	NM_030984	TBXAS1	NM_030984	Homo sapiens thromboxane A synthase 1 (platelet, cytochrome P450, family 5, subfamily A) (TBXAS1), transcript variant TXS-II, mRNA [NM_030984]	chr7	GO:0001516(prostaglandin biosynthetic process);GO:0006118(electron transport);GO:0006633(fatty acid biosynthetic process);GO:0007596(blood coagulation)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0004796(thromboxane-A synthase activity);GO:0005506(iron ion binding);GO:0016712(oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, reduced flavin or flavoprotein as one donor, and incorporation of one atom of oxygen);GO:0016853(isomerase activity);GO:0020037(heme binding);GO:0046872(metal ion binding)
A_23_P124927	NM_006480	RGS14	NM_006480	Homo sapiens regulator of G-protein signalling 14 (RGS14), mRNA [NM_006480]	chr5	GO:0007165(signal transduction);GO:0008277(regulation of G-protein coupled receptor protein signaling pathway);GO:0009968(negative regulation of signal transduction)		GO:0005057(receptor signaling protein activity);GO:0005096(GTPase activator activity)
A_23_P160377	NM_003462	DNALI1	NM_003462	Homo sapiens dynein, axonemal, light intermediate chain 1 (DNALI1), mRNA [NM_003462]	chr1	GO:0006928(cell motility);GO:0007338(single fertilization)	GO:0005858(axonemal dynein complex);GO:0005930(axoneme)	GO:0003777(microtubule motor activity)
A_32_P167212	A_32_P167212	A_32_P167212			chr6			
A_24_P200420	NM_014331	SLC7A11	NM_014331	Homo sapiens solute carrier family 7, (cationic amino acid transporter, y+ system) member 11 (SLC7A11), mRNA [NM_014331]	chr4	GO:0006461(protein complex assembly);GO:0006810(transport);GO:0006865(amino acid transport)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0015171(amino acid transporter activity);GO:0015327(cystine:glutamate antiporter activity);GO:0015359(amino acid permease activity)
A_23_P7882	BC022217	C6orf85	BC022217	Homo sapiens chromosome 6 open reading frame 85, mRNA (cDNA clone IMAGE:3846727), complete cds. [BC022217]	chr6	GO:0006810(transport)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005215(transporter activity)
A_23_P417415	NM_147161	ACOT11	NM_147161	Homo sapiens acyl-CoA thioesterase 11 (ACOT11), transcript variant 2, mRNA [NM_147161]	chr1	GO:0006631(fatty acid metabolic process);GO:0007242(intracellular signaling cascade);GO:0009266(response to temperature stimulus)	GO:0005737(cytoplasm)	GO:0004759(serine esterase activity);GO:0016291(acyl-CoA thioesterase activity);GO:0016787(hydrolase activity)
A_24_P164718	NM_016496	2-Mar	NM_016496	Homo sapiens membrane-associated ring finger (C3HC4) 2 (MARCH2), transcript variant 1, mRNA [NM_016496]	chr19	GO:0006512(ubiquitin cycle);GO:0006897(endocytosis)	GO:0005764(lysosome);GO:0005783(endoplasmic reticulum);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0016874(ligase activity);GO:0046872(metal ion binding)
A_23_P92899	NM_031908	C1QTNF2	NM_031908	Homo sapiens C1q and tumor necrosis factor related protein 2 (C1QTNF2), mRNA [NM_031908]	chr5	GO:0000187(activation of MAPK activity);GO:0006817(phosphate transport);GO:0045725(positive regulation of glycogen biosynthetic process);GO:0046321(positive regulation of fatty acid oxidation);GO:0046326(positive regulation of glucose import);GO:0051260(protein homooligomerization)	GO:0005737(cytoplasm)	GO:0005102(receptor binding)
A_23_P26783	NM_002809	PSMD3	NM_002809	Homo sapiens proteasome (prosome, macropain) 26S subunit, non-ATPase, 3 (PSMD3), mRNA [NM_002809]	chr17		GO:0000502(proteasome complex (sensu Eukaryota));GO:0005829(cytosol);GO:0043234(protein complex)	GO:0005515(protein binding)

A_23_P250164	NM_000187	HGD	NM_000187	Homo sapiens homogentisate 1,2-dioxygenase (homogentisate oxidase) (HGD), mRNA [NM_000187]	chr3	GO:0006559(L-phenylalanine catabolic process);GO:0006572(tyrosine catabolic process)		GO:0004411(homogentisate 1,2-dioxygenase activity);GO:0005506(iron ion binding);GO:0016491(oxidoreductase activity);GO:0046872(metal ion binding)
A_23_P50498	NM_000146	FTL	NM_000146	Homo sapiens ferritin, light polypeptide (FTL), mRNA [NM_000146]	chr19	GO:0006826(iron ion transport);GO:0006879(iron ion homeostasis)	GO:0008043(ferritin complex)	GO:0005488(binding);GO:0008199(ferric iron binding);GO:0016491(oxidoreductase activity);GO:0042802(identical protein binding)
A_23_P332399	NM_016315	GULP1	NM_016315	Homo sapiens GULP, engulfment adaptor PTB domain containing 1 (GULP1), mRNA [NM_016315]	chr2	GO:0006911(phagocytosis, engulfment);GO:0006915(apoptosis)		GO:0004871(signal transducer activity);GO:0005515(protein binding)
A_23_P104876	NM_017425	SPA17	NM_017425	Homo sapiens sperm autoantigenic protein 17 (SPA17), mRNA [NM_017425]	chr11	GO:0007165(signal transduction);GO:0007283(spermatogenesis);GO:0007338(single fertilization);GO:0007339(binding of sperm to zona pellucida)	GO:0016020(membrane)	GO:0008603(cAMP-dependent protein kinase regulator activity)
A_23_P140748	NM_022910	NDRG4	NM_022910	Homo sapiens NDRG family member 4 (NDRG4), mRNA [NM_022910]	chr16	GO:0006950(response to stress);GO:0007275(multicellular organismal development);GO:0016049(cell growth);GO:0030154(cell differentiation)	GO:0005737(cytoplasm)	
A_23_P54918	NM_153486	LDHD	NM_153486	Homo sapiens lactate dehydrogenase D (LDHD), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA [NM_153486]	chr16	GO:0006118(electron transport);GO:0006754(ATP biosynthetic process)	GO:0005739(mitochondrion)	GO:0004458(D-lactate dehydrogenase (cytochrome) activity);GO:0005515(protein binding);GO:0008720(D-lactate dehydrogenase activity);GO:0016491(oxidoreductase activity)
A_23_P205713	NM_014178	STXBP6	NM_014178	Homo sapiens syntaxin binding protein 6 (amisyn) (STXBP6), mRNA [NM_014178]	chr14	GO:0016192(vesicle-mediated transport)	GO:0016021(integral to membrane)	
A_23_P138465	NM_004741	NOLC1	NM_004741	Homo sapiens nucleolar and coiled-body phosphoprotein 1 (NOLC1), mRNA [NM_004741]	chr10	GO:0006364(rRNA processing);GO:0007049(cell cycle);GO:0007067(mitosis)	GO:0005634(nucleus);GO:0005730(nucleolus);GO:0005737(cytoplasm)	GO:0000166(nucleotide binding);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0005525(GTP binding)
A_23_P151915	ENST00000267857	GCNT3		glucosaminyl (N-acetyl) transferase 3, mucin type [Source:RefSeq_peptide;Acc:NP_004742] [ENST00000267857]	chr15	GO:0005975(carbohydrate metabolic process);GO:0006493(protein amino acid O-linked glycosylation)	GO:0005624(membrane fraction);GO:0016020(membrane)	GO:0003829(beta-1,3-galactosyl-O-glycosyl-glycoprotein beta-1,6-N-acetylglucosaminyltransferase activity);GO:0008109(N-acetyllactosaminide beta-1,6-N-acetylglucosaminyltransferase activity);GO:0016757(transferase activity, transferring glycosyl groups)
A_23_P32233	NM_004235	KLF4	NM_004235	Homo sapiens Kruppel-like factor 4 (gut) (KLF4), mRNA [NM_004235]	chr9	GO:0006350(transcription);GO:0007500(mesodermal cell fate determination);GO:0008285(negative regulation of cell proliferation);GO:0045892(negative regulation of transcription, DNA-dependent)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003676(nucleic acid binding);GO:0003700(transcription factor activity);GO:0008270(zinc ion binding);GO:0016563(transcriptional activator activity);GO:0016564(transcriptional repressor activity);GO:0046872(metal ion binding)
A_23_P67224	NM_003811	TNFSF9	NM_003811	Homo sapiens tumor necrosis factor (ligand) superfamily, member 9 (TNFSF9), mRNA [NM_003811]	chr19	GO:0006915(apoptosis);GO:0006955(immune response);GO:0007165(signal transduction);GO:0007267(cell-cell signaling);GO:0008283(cell proliferation)	GO:0005615(extracellular space);GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0005125(cytokine activity);GO:0005164(tumor necrosis factor receptor binding)
A_23_P88163	NM_018036	C14orf103	NM_018036	Homo sapiens chromosome 14 open reading frame 103 (C14orf103), mRNA [NM_018036]	chr14			
A_23_P409623	NM_003621	PPFIBP2	NM_003621	Homo sapiens PTPRF interacting protein, binding protein 2 (liprin beta 2) (PPFIBP2), mRNA [NM_003621]	chr11	GO:0007154(cell communication)	GO:0005622(intracellular)	GO:0003674(molecular_function)
A_23_P61371	NM_198282	TMEM173	NM_198282	Homo sapiens transmembrane protein 173 (TMEM173), mRNA [NM_198282]	chr5		GO:0016020(membrane);GO:0016021(integral to membrane)	
A_23_P144096	NM_145071	CISH	NM_145071	Homo sapiens cytokine inducible SH2-containing protein (CISH), mRNA [NM_145071]	chr3	GO:0001558(regulation of cell growth);GO:0007242(intracellular signaling cascade);GO:0009968(negative regulation of signal transduction)	GO:0005575(cellular_component)	GO:0003674(molecular_function)
A_23_P44569	NM_000392	ABCC2	NM_000392	Homo sapiens ATP-binding cassette, sub-family C (CFTR/MRP), member 2 (ABCC2), mRNA [NM_000392]	chr10	GO:0006810(transport)	GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0000166(nucleotide binding);GO:0005215(transporter activity);GO:0005524(ATP binding);GO:0008514(organic anion transporter activity);GO:0016887(ATPase activity);GO:0042626(ATPase activity, coupled to transmembrane movement of substances)
A_23_P304524	NM_001040260	DCLK2	NM_001040260	Homo sapiens doublecortin and CaM kinase-like 2 (DCAMKL2), transcript variant 1, mRNA [NM_001040260]	chr4	GO:0006468(protein amino acid phosphorylation);GO:0007242(intracellular signaling cascade)		GO:0000166(nucleotide binding);GO:0004674(protein serine/threonine kinase activity);GO:0005524(ATP binding);GO:0016740(transferase activity)
A_23_P329870	NM_024599	RHBDF2	NM_024599	Homo sapiens rhomboid 5 homolog 2 (Drosophila) (RHBDF2), transcript variant 1, mRNA [NM_024599]	chr17		GO:0016021(integral to membrane)	
A_23_P212339	NM_024513	FYCO1	NM_024513	Homo sapiens FYVE and coiled-coil domain containing 1 (FYCO1), mRNA [NM_024513]	chr3	GO:0006810(transport)	GO:0016021(integral to membrane)	GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P56050	BC107798	TNNT1	BC107798	Homo sapiens troponin T type 1 (skeletal, slow), mRNA (cDNA clone MGC:104241 IMAGE:4247379), complete cds. [BC107798]	chr19	GO:0006937(regulation of muscle contraction)		GO:0005515(protein binding);GO:0005523(tropomyosin binding)
A_32_P111524	BC033539	BC033539	BC033539	Homo sapiens cDNA clone IMAGE:4819052. [BC033539]	chr12			
A_23_P142631	NM_054033	FKBP1B	NM_054033	Homo sapiens FK506 binding protein 1B, 12.6 kDa (FKBP1B), transcript variant 2, mRNA [NM_054033]	chr2	GO:0006457(protein folding);GO:0006936(muscle contraction)	GO:0005737(cytoplasm)	GO:0003755(peptidyl-prolyl cis-trans isomerase activity);GO:0016853(isomerase activity)

A_32_P98979	BE467780	BE467780	BE467780	hz74a10.x1 NCI_CGAP_Lu24 Homo sapiens cDNA clone IMAGE:3213690 3', mRNA sequence [BE467780]	chr1			
A_23_P203564	NM_003442	ZNF143	NM_003442	Homo sapiens zinc finger protein 143 (ZNF143), mRNA [NM_003442]	chr11	GO:0006350(transcription);GO:0006357(regulation of transcription from RNA polymerase II promoter);GO:0006359(regulation of transcription from RNA polymerase III promoter)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0003704(specific RNA polymerase II transcription factor activity);GO:0003709(RNA polymerase III transcription factor activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P146084	NM_000637	GSR	NM_000637	Homo sapiens glutathione reductase (GSR), mRNA [NM_000637]	chr8	GO:0006118(electron transport);GO:0006749(glutathione metabolic process);GO:0045454(cell redox homeostasis)	GO:0005737(cytoplasm);GO:0005739(mitochondrion)	GO:0004362(glutathione-disulfide reductase activity);GO:0050660(FAD binding);GO:0050661(NADP binding)
A_32_P183609	NM_001040445	ASB1	NM_001040445	Homo sapiens ankyrin repeat and SOCS box-containing 1 (ASB1), mRNA [NM_001040445]	chr2	GO:0007242(intracellular signaling cascade);GO:0007275(multicellular organismal development);GO:0030539(male genitalia development);GO:0042036(negative regulation of cytokine biosynthetic process)	GO:0005622(intracellular)	GO:0003674(molecular_function)
A_23_P87216	NM_002394	SLC3A2	NM_002394	Homo sapiens solute carrier family 3 (activators of dibasic and neutral amino acid transport), member 2 (SLC3A2), transcript variant 3, mRNA [NM_002394]	chr11	GO:0005975(carbohydrate metabolic process);GO:0006810(transport);GO:0006816(calcium ion transport);GO:0006865(amino acid transport);GO:0015827(tryptophan transport);GO:0016049(cell growth)	GO:0009986(cell surface);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0003824(catalytic activity);GO:0005432(calcium:sodium antiporter activity);GO:0005515(protein binding);GO:0015171(amino acid transporter activity);GO:0043169(cation binding)
A_24_P64100	AF495725	SLC25A37	AF495725	Homo sapiens FP15737 mRNA, complete cds. [AF495725]	chr8	GO:0006811(ion transport);GO:0048250(mitochondrial iron ion transport)	GO:0005739(mitochondrion);GO:0005743(mitochondrial inner membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005381(iron ion transporter activity);GO:0005488(binding);GO:0005506(iron ion binding)
A_24_P335263	NM_199040	NUDT4	NM_199040	Homo sapiens nudix (nucleoside diphosphate linked moiety X)-type motif 4 (NUDT4), transcript variant 2, mRNA [NM_199040]	chr12	GO:0007242(intracellular signaling cascade);GO:0009187(cyclic nucleotide metabolic process);GO:0019722(calcium-mediated signaling);GO:0019935(cyclic-nucleotide-mediated signaling);GO:0046831(regulation of RNA export from nucleus);GO:0046907(intracellular transport)	GO:0005622(intracellular)	GO:0000287(magnesium ion binding);GO:0008486(diphosphoinositol-polyphosphate diphosphatase activity);GO:0016787(hydrolase activity);GO:0030145(manganese ion binding)
A_23_P305759	NM_138340	ABHD3	NM_138340	Homo sapiens abhydrolase domain containing 3 (ABHD3), mRNA [NM_138340]	chr18		GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0004759(serine esterase activity);GO:0016787(hydrolase activity)
A_23_P121082	NM_000158	GBE1	NM_000158	Homo sapiens glucan (1,4-alpha-), branching enzyme 1 (glycogen branching enzyme, Andersen disease, glycogen storage disease type IV) (GBE1), mRNA [NM_000158]	chr3	GO:0005975(carbohydrate metabolic process);GO:0005978(glycogen biosynthetic process);GO:0006091(generation of precursor metabolites and energy)		GO:0003844(1,4-alpha-glucan branching enzyme activity);GO:0004553(hydrolase activity, hydrolyzing O-glycosyl compounds);GO:0016757(transferase activity, transferring glycosyl groups);GO:0043169(cation binding)
A_24_P36868	NM_025160	WDR26	NM_025160	Homo sapiens WD repeat domain 26 (WDR26), mRNA [NM_025160]	chr1		GO:0005737(cytoplasm)	
A_23_P22614	NM_145802	6-Sep	NM_145802	Homo sapiens septin 6 (SEPT6), transcript variant V, mRNA [NM_145802]	chrX	GO:0000910(cytokinesis);GO:0007049(cell cycle)	GO:0005575(cellular_component)	GO:0000166(nucleotide binding);GO:0005515(protein binding);GO:0005525(GTP binding)
A_23_P77049	NM_152333	SLC25A29	NM_152333	Homo sapiens solute carrier family 25, member 29 (SLC25A29), transcript variant 2, mRNA [NM_152333]	chr14	GO:0006810(transport)	GO:0005739(mitochondrion);GO:0005743(mitochondrial inner membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005215(transporter activity);GO:0005488(binding)
A_23_P207507	NM_003786	ABCC3	NM_003786	Homo sapiens ATP-binding cassette, sub-family C (CFTR/MRP), member 3 (ABCC3), mRNA [NM_003786]	chr17	GO:0006810(transport)	GO:0005624(membrane fraction);GO:0005887(integral to plasma membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0000166(nucleotide binding);GO:0005215(transporter activity);GO:0005524(ATP binding);GO:0008514(organic anion transporter activity);GO:0016887(ATPase activity);GO:0042626(ATPase activity, coupled to transmembrane movement of substances)
A_23_P55998	NM_005628	SLC1A5	NM_005628	Homo sapiens solute carrier family 1 (neutral amino acid transporter), member 5 (SLC1A5), mRNA [NM_005628]	chr19	GO:0006810(transport);GO:0006835(dicarboxylic acid transport);GO:0015804(neutral amino acid transport)	GO:0005624(membrane fraction);GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0004872(receptor activity);GO:0005515(protein binding);GO:0015175(neutral amino acid transporter activity);GO:0015293(symporter activity);GO:0017153(sodium:dicarboxylate symporter activity)
A_23_P127033	NM_024693	ECHDC3	NM_024693	Homo sapiens enoyl Coenzyme A hydratase domain containing 3 (ECHDC3), mRNA [NM_024693]	chr10	GO:0008152(metabolic process)		GO:0003824(catalytic activity)
A_23_P147388	NM_015254	KIF13B	NM_015254	Homo sapiens kinesin family member 13B (KIF13B), mRNA [NM_015254]	chr8	GO:0006605(protein targeting);GO:0007018(microtubule-based movement);GO:0007165(signal transduction);GO:0042110(T cell activation)	GO:0005737(cytoplasm);GO:0005856(cytoskeleton);GO:0005874(microtubule);GO:0005875(microtubule associated complex)	GO:0000166(nucleotide binding);GO:0003777(microtubule motor activity);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0019901(protein kinase binding)
A_24_P150874	BX647930	BX647930	BX647930	Homo sapiens mRNA; cDNA DKFZp686I20201 (from clone DKFZp686I20201). [BX647930]	chr17			
A_32_P151933	THC2638232	THC2638232		Q7RQ28_PLAYO (Q7RQ28) Nuclear protein snf7, partial (7%) [THC2638232]	chr18			
A_23_P132956	NM_004181	UCHL1	NM_004181	Homo sapiens ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase) (UCHL1), mRNA [NM_004181]	chr4	GO:0006511(ubiquitin-dependent protein catabolic process);GO:0016579(protein deubiquitination)	GO:0005622(intracellular);GO:0005737(cytoplasm)	GO:0004197(cysteine-type endopeptidase activity);GO:0004221(ubiquitin thiolesterase activity);GO:0005515(protein binding);GO:0008242(omega peptidase activity);GO:0016874(ligase activity);GO:0043130(ubiquitin binding)
A_24_P329795	NM_007021	C10orf10	NM_007021	Homo sapiens chromosome 10 open reading frame 10 (C10orf10), mRNA [NM_007021]	chr10		GO:0005739(mitochondrion)	
A_23_P255331	NM_032623	OSAP	NM_032623	Homo sapiens ovary-specific acidic protein (OSAP), mRNA [NM_032623]	chr4			

A_23_P75811	NM_002394	SLC3A2	NM_002394	Homo sapiens solute carrier family 3 (activators of dibasic and neutral amino acid transport), member 2 (SLC3A2), transcript variant 3, mRNA [NM_002394]	chr11	GO:0005975(carbohydrate metabolic process);GO:0006810(transport);GO:0006816(calcium ion transport);GO:0006865(amino acid transport);GO:0015827(tryptophan transport);GO:0016049(cell growth)	GO:0009986(cell surface);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0003824(catalytic activity);GO:0005432(calcium:sodium antiporter activity);GO:0005515(protein binding);GO:0015171(amino acid transporter activity);GO:0043169(cation binding)
A_24_P206344	NM_152557	ZNF746	NM_152557	Homo sapiens zinc finger protein 746 (ZNF746), mRNA [NM_152557]	chr7	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003676(nucleic acid binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P137035	NM_003662	PIR	NM_003662	Homo sapiens pirin (iron-binding nuclear protein) (PIR), transcript variant 1, mRNA [NM_003662]	chrX	GO:0006366(transcription from RNA polymerase II promoter)	GO:0005634(nucleus)	GO:0003712(transcription cofactor activity);GO:0005506(iron ion binding);GO:0046872(metal ion binding)
A_32_P116556	AB058761	ZNF469	AB058761	Homo sapiens mRNA for KIAA1858 protein, partial cds. [AB058761]	chr16	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003676(nucleic acid binding);GO:0003677(DNA binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_32_P4882	A_32_P4882	A_32_P4882			chr4			
A_23_P324340	NM_033510	DISP2	NM_033510	Homo sapiens dispatched homolog 2 (Drosophila) (DISP2), mRNA [NM_033510]	chr15			
A_23_P216094	NM_004318	ASPH	NM_004318	Homo sapiens aspartate beta-hydroxylase (ASPH), transcript variant 1, mRNA [NM_004318]	chr8	GO:0006936(muscle contraction);GO:0008150(biological_process);GO:0018193(peptidyl-amino acid modification)	GO:0005783(endoplasmic reticulum);GO:0005789(endoplasmic reticulum membrane);GO:0016020(membrane);GO:0016021(integral to membrane);GO:0030176(integral to endoplasmic reticulum membrane)	GO:0004597(peptide-aspartate beta-dioxygenase activity);GO:0005488(binding);GO:0005506(iron ion binding);GO:0005509(calcium ion binding);GO:0008307(structural constituent of muscle);GO:0009055(electron carrier activity);GO:0016702(oxidoreductase activity, acting on single donors with incorporation of molecular oxygen, incorporation of two atoms of oxygen)
A_23_P373054	NM_173826	C3orf23	NM_173826	Homo sapiens chromosome 3 open reading frame 23 (C3orf23), transcript variant 1, mRNA [NM_173826]	chr3		GO:0005739(mitochondrion)	
A_24_P18105	NM_032466	ASPH	NM_032466	Homo sapiens aspartate beta-hydroxylase (ASPH), transcript variant 3, mRNA [NM_032466]	chr8	GO:0006936(muscle contraction);GO:0008150(biological_process);GO:0018193(peptidyl-amino acid modification)	GO:0005783(endoplasmic reticulum);GO:0005789(endoplasmic reticulum membrane);GO:0016020(membrane);GO:0016021(integral to membrane);GO:0030176(integral to endoplasmic reticulum membrane)	GO:0004597(peptide-aspartate beta-dioxygenase activity);GO:0005488(binding);GO:0005506(iron ion binding);GO:0005509(calcium ion binding);GO:0008307(structural constituent of muscle);GO:0009055(electron carrier activity);GO:0016702(oxidoreductase activity, acting on single donors with incorporation of molecular oxygen, incorporation of two atoms of oxygen)
A_23_P62139	NM_005710	PQBP1	NM_005710	Homo sapiens polyglutamine binding protein 1 (PQBP1), transcript variant 1, mRNA [NM_005710]	chrX	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent)	GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0003713(transcription coactivator activity)
A_23_P6762	NM_032492	JAGN1	NM_032492	Homo sapiens jagunal homolog 1 (Drosophila) (JAGN1), mRNA [NM_032492]	chr3			
A_32_P108826	NM_194314	ZBTB41	NM_194314	Homo sapiens zinc finger and BTB domain containing 41 (ZBTB41), mRNA [NM_194314]	chr1	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_32_P64570	NM_153186	ANKRD15	NM_153186	Homo sapiens ankyrin repeat domain 15 (ANKRD15), transcript variant 2, mRNA [NM_153186]	chr9	GO:0007049(cell cycle);GO:0045786(negative regulation of progression through cell cycle)		
A_23_P119141	NM_203500	KEAP1	NM_203500	Homo sapiens kelch-like ECH-associated protein 1 (KEAP1), transcript variant 1, mRNA [NM_203500]	chr19	GO:0001701(in utero embryonic development);GO:0006355(regulation of transcription, DNA-dependent);GO:0045604(regulation of epidermal cell differentiation)	GO:0005634(nucleus);GO:0005737(cytoplasm);GO:0005783(endoplasmic reticulum)	GO:0005515(protein binding);GO:0030528(transcription regulator activity)
A_24_P916288	AK026497	AK026497	AK026497	Homo sapiens cDNA: FLJ22844 fis, clone KAIA5181. [AK026497]	chr14			
A_23_P353704	NM_019593	RP5-1022P6.2	NM_019593	Homo sapiens hypothetical protein KIAA1434 (KIAA1434), mRNA [NM_019593]	chr20			
A_23_P95125	A_23_P95125	A_23_P95125						
A_23_P39766	NM_014905	GLS	NM_014905	Homo sapiens glutaminase (GLS), mRNA [NM_014905]	chr2	GO:0006543(glutamine catabolic process)	GO:0005739(mitochondrion)	GO:0004359(glutaminase activity);GO:0016787(hydrolase activity)
A_23_P209394	AF009616	CFLAR	AF009616	Homo sapiens FLAME-1 mRNA, complete cds. [AF009616]	chr2	GO:0006508(proteolysis);GO:0006916(anti-apoptosis);GO:0008624(induction of apoptosis by extracellular signals);GO:0042981(regulation of apoptosis);GO:0043123(positive regulation of I-kappaB kinase/NF-kappaB cascade)		GO:0004871(signal transducer activity);GO:0005515(protein binding);GO:0030693(caspase activity)
A_23_P206396	NM_016951	CKLF	NM_016951	Homo sapiens chemokine-like factor (CKLF), transcript variant 1, mRNA [NM_016951]	chr16	GO:0006935(chemotaxis);GO:0008283(cell proliferation);GO:0030593(neutrophil chemotaxis);GO:0045045(secretory pathway);GO:0048246(macrophage chemotaxis);GO:0048247(lymphocyte chemotaxis)	GO:0005576(extracellular region);GO:0005615(extracellular space);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0008009(chemokine activity)
A_23_P10542	NM_053044	HTRA3	NM_053044	Homo sapiens HtrA serine peptidase 3 (HTRA3), mRNA [NM_053044]	chr4	GO:0001558(regulation of cell growth);GO:0006508(proteolysis)	GO:0005576(extracellular region)	GO:0004252(serine-type endopeptidase activity);GO:0005515(protein binding);GO:0005520(insulin-like growth factor binding);GO:0008233(peptidase activity)
A_24_P825942	AK001796	LOC541471	AK001796	Homo sapiens cDNA FLJ10934 fis, clone OVARC1000640. [AK001796]	chr2			
A_23_P7212	NM_000204	CFI	NM_000204	Homo sapiens complement factor I (CFI), mRNA [NM_000204]	chr4	GO:0006508(proteolysis);GO:0006958(complement activation, classical pathway);GO:0045087(innate immune response)	GO:0005576(extracellular region);GO:0016020(membrane)	GO:0003818(complement factor I activity);GO:0004252(serine-type endopeptidase activity);GO:0005044(scavenger receptor activity);GO:0008233(peptidase activity)
A_23_P318284	NM_015141	GPD1L	NM_015141	Homo sapiens glycerol-3-phosphate dehydrogenase 1-like (GPD1L), mRNA [NM_015141]	chr3	GO:0005975(carbohydrate metabolic process);GO:0046168(glycerol-3-phosphate catabolic process)	GO:0005737(cytoplasm);GO:0009331(glycerol-3-phosphate dehydrogenase complex)	GO:0004367(glycerol-3-phosphate dehydrogenase (NAD+) activity);GO:0051287(NAD binding)

A_23_P69908	NM_002064	GLRX	NM_002064	Homo sapiens glutaredoxin (thioltransferase) (GLRX), mRNA [NM_002064]	chr5	GO:0006118(electron transport);GO:0006810(transport);GO:0045454(cell redox homeostasis)	GO:0005829(cytosol)	GO:0009055(electron carrier activity);GO:0015035(protein disulfide oxidoreductase activity);GO:0015038(glutathione disulfide oxidoreductase activity);GO:0047485(protein N-terminus binding)
A_23_P64404	NM_021727	FADS3	NM_021727	Homo sapiens fatty acid desaturase 3 (FADS3), mRNA [NM_021727]	chr11	GO:0006629(lipid metabolic process);GO:0006633(fatty acid biosynthetic process);GO:0006636(fatty acid desaturation)	GO:0005624(membrane fraction);GO:0016020(membrane)	GO:0003674(molecular_function);GO:0005506(iron ion binding);GO:0016491(oxidoreductase activity);GO:0016717(oxidoreductase activity, acting on paired donors, with oxidation of a pair of donors resulting in the reduction of molecular oxygen to two molecules of water);GO:0020037(heme binding);GO:0046914(transition metal ion binding)
A_32_P208403	NM_053064	GNG2	NM_053064	Homo sapiens guanine nucleotide binding protein (G protein), gamma 2 (GNG2), mRNA [NM_053064]	chr14	GO:0007165(signal transduction);GO:0007186(G-protein coupled receptor protein signaling pathway);GO:0008283(cell proliferation)	GO:0005834(heterotrimeric G-protein complex);GO:0016020(membrane)	GO:0004871(signal transducer activity)
A_24_P40551	NM_001080425	BEXL1	NM_001080425	Homo sapiens brain expressed X-linked-like 1 (BEXL1), mRNA [NM_001080425]	chrX		GO:0005634(nucleus)	
A_23_P390744	NM_144600	C16orf63	NM_144600	Homo sapiens chromosome 16 open reading frame 63 (C16orf63), mRNA [NM_144600]	chr16			
A_23_P91140	NM_018441	PECR	NM_018441	Homo sapiens peroxisomal trans-2-enoyl-CoA reductase (PECR), mRNA [NM_018441]	chr2	GO:0006633(fatty acid biosynthetic process);GO:0008152(metabolic process);GO:0042981(regulation of apoptosis)	GO:0005739(mitochondrion);GO:0005777(peroxisome)	GO:0016491(oxidoreductase activity);GO:0019166(trans-2-enoyl-CoA reductase (NADPH) activity)
A_23_P128967	NM_005589	ALDH6A1	NM_005589	Homo sapiens aldehyde dehydrogenase 6 family, member A1 (ALDH6A1), nuclear gene encoding mitochondrial protein, mRNA [NM_005589]	chr14	GO:0006220(pyrimidine nucleotide metabolic process);GO:0006573(valine metabolic process);GO:0008152(metabolic process);GO:0019859(thymine metabolic process)	GO:0005739(mitochondrion)	GO:0000062(acyl-CoA binding);GO:0004491(methylmalonate-semialdehyde dehydrogenase (acylating) activity);GO:0016491(oxidoreductase activity);GO:0018478(malonate-semialdehyde dehydrogenase (acetylating) activity)
A_23_P374322	NM_153218	C13orf31	NM_153218	Homo sapiens chromosome 13 open reading frame 31 (C13orf31), mRNA [NM_153218]	chr13			
A_32_P42684	NM_014331	SLC7A11	NM_014331	Homo sapiens solute carrier family 7, (cationic amino acid transporter, y+ system) member 11 (SLC7A11), mRNA [NM_014331]	chr4	GO:0006461(protein complex assembly);GO:0006810(transport);GO:0006865(amino acid transport)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0015171(amino acid transporter activity);GO:0015327(cystine:glutamate antiporter activity);GO:0015359(amino acid permease activity)
A_23_P136724	BX640843	LOC344887	BX640843	Homo sapiens mRNA; cDNA DKFZp686B14224 (from clone DKFZp686B14224). [BX640843]	chr3			
A_32_P157671	A_32_P157671	A_32_P157671			chr17			
A_23_P45475	NM_000169	GLA	NM_000169	Homo sapiens galactosidase, alpha (GLA), mRNA [NM_000169]	chrX	GO:0008152(metabolic process);GO:0009311(oligosaccharide metabolic process);GO:0045019(negative regulation of nitric oxide biosynthetic process);GO:0046479(glycosphingolipid catabolic process);GO:0051001(negative regulation of nitric-oxide synthase activity)	GO:0005576(extracellular region);GO:0005737(cytoplasm);GO:0005764(lysosome);GO:0005794(Golgi apparatus)	GO:0004553(hydrolase activity, hydrolyzing O-glycosyl compounds);GO:0004557(alpha-galactosidase activity);GO:0005102(receptor binding);GO:0042803(protein homodimerization activity);GO:0043169(cation binding)
A_23_P10232	NM_017935	BANK1	NM_017935	Homo sapiens B-cell scaffold protein with ankyrin repeats 1 (BANK1), mRNA [NM_017935]	chr4	GO:0042113(B cell activation)		
A_23_P78685	NM_004461	FARSA	NM_004461	Homo sapiens phenylalanyl-tRNA synthetase, alpha subunit (FARSA), mRNA [NM_004461]	chr19	GO:0006432(phenylalanyl-tRNA aminoacylation)	GO:0005625(soluble fraction);GO:0005737(cytoplasm)	GO:0000166(nucleotide binding);GO:0004826(phenylalanine-tRNA ligase activity);GO:0005524(ATP binding);GO:0016874(ligase activity)
A_23_P129389	NM_017740	ZDHHC7	NM_017740	Homo sapiens zinc finger, DHHC-type containing 7 (ZDHHC7), mRNA [NM_017740]	chr16		GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0008415(acyltransferase activity);GO:0016740(transferase activity);GO:0046872(metal ion binding)
A_23_P19219	NM_014034	ASF1A	NM_014034	Homo sapiens ASF1 anti-silencing function 1 homolog A (S. cerevisiae) (ASF1A), mRNA [NM_014034]	chr6	GO:0006281(DNA repair);GO:0006333(chromatin assembly or disassembly);GO:0006334(nucleosome assembly);GO:0006345(loss of chromatin silencing);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006457(protein folding);GO:0016568(chromatin modification)	GO:0005634(nucleus);GO:0016585(chromatin remodeling complex)	GO:0003682(chromatin binding);GO:0042393(histone binding)
A_32_P177953	ENST00000370238	GCLM		Glutamate--cysteine ligase regulatory subunit (EC 6.3.2.2) (Gamma- glutamylcysteine synthetase) (Gamma-ECS) (GCS light chain) (Glutamate--cysteine ligase modifier subunit). [Source:Uniprot/SWISSPROT;Acc:P48507] [ENST00000370238]	chr1	GO:0006534(cysteine metabolic process);GO:0006536(glutamate metabolic process);GO:0006749(glutathione metabolic process);GO:0006750(glutathione biosynthetic process);GO:0006979(response to oxidative stress);GO:0035229(positive regulation of glutamate-cysteine ligase activity);GO:0042493(response to drug);GO:0050880(regulation of blood vessel size)	GO:0005625(soluble fraction);GO:0005829(cytosol);GO:0017109(glutamate-cysteine ligase complex)	GO:0004357(glutamate-cysteine ligase activity);GO:0005515(protein binding);GO:0016491(oxidoreductase activity);GO:0016874(ligase activity);GO:0035226(glutamate-cysteine ligase catalytic subunit binding);GO:0046982(protein heterodimerization activity)
A_23_P215658	NM_030900	TBRG4	NM_030900	Homo sapiens transforming growth factor beta regulator 4 (TBRG4), transcript variant 2, mRNA [NM_030900]	chr7	GO:0006915(apoptosis)	GO:0005739(mitochondrion)	GO:0004672(protein kinase activity);GO:0005524(ATP binding)
A_24_P887092	THC2645879	THC2645879			chr11			

A_23_P105307	NM_201444	DGKA	NM_201444	Homo sapiens diacylglycerol kinase, alpha 80kDa (DGKA), transcript variant 1, mRNA [NM_201444]	chr12	GO:0007205(protein kinase C activation);GO:0007242(intracellular signaling cascade);GO:0008150(biological_process)	GO:0005575(cellular_component);GO:0005829(cytosol);GO:0005886(plasma membrane)	GO:0004143(diacylglycerol kinase activity);GO:0005509(calcium ion binding);GO:0005543(phospholipid binding);GO:0008270(zinc ion binding);GO:0016301(kinase activity);GO:0016740(transferase activity);GO:0019992(diacylglycerol binding)
A_23_P356581	NM_022370	ROBO3	NM_022370	Homo sapiens roundabout, axon guidance receptor, homolog 3 (Drosophila) (ROBO3), mRNA [NM_022370]	chr11	GO:0006935(chemotaxis);GO:0007275(multicellular organismal development);GO:0007399(nervous system development);GO:0007411(axon guidance);GO:0030154(cell differentiation)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0004872(receptor activity)
A_24_P46659	ENST00000316149	C6orf66		UPF0240 protein C6orf66. [Source:Uniprot/SWISSPROT;Acc:Q9P032] [ENST00000316149]	chr6			
A_23_P163306	NM_032866	CGNL1	NM_032866	Homo sapiens cingulin-like 1 (CGNL1), mRNA [NM_032866]	chr15		GO:0016459(myosin complex)	GO:0003774(motor activity)
A_23_P154962	BC035246	KIAA1666	BC035246	Homo sapiens KIAA1666 protein, mRNA (cDNA clone IMAGE:4827837), complete cds. [BC035246]	chr22	GO:0008152(metabolic process)		GO:0016491(oxidoreductase activity);GO:0046914(transition metal ion binding)
A_23_P134395	NM_012453	TBL2	NM_012453	Homo sapiens transducin (beta)-like 2 (TBL2), mRNA [NM_012453]	chr7	GO:0008150(biological_process)	GO:0005575(cellular_component)	GO:0003674(molecular_function)
A_24_P283225	NM_004999	MYO6	NM_004999	Homo sapiens myosin VI (MYO6), mRNA [NM_004999]	chr6	GO:0006886(intracellular protein transport);GO:0006897(endocytosis);GO:0007605(sensory perception of sound);GO:0008150(biological_process);GO:0030048(actin filament-based movement);GO:0030330(DNA damage response, signal transduction by p53 class mediator);GO:0045944(positive regulation of transcription from RNA polymerase II promoter);GO:0051046(regulation of secretion)	GO:0001726(ruffle);GO:0005634(nucleus);GO:0005654(nucleoplasm);GO:0005737(cytoplasm);GO:0005794(Golgi apparatus);GO:0005905(coated pit);GO:0005938(cell cortex);GO:0016020(membrane);GO:0016461(unconventional myosin complex);GO:0016591(DNA-directed RNA polymerase II, holoenzyme);GO:0045334(clathrin-coated endocytic vesicle);GO:0048471(perinuclear region of cytoplasm)	GO:0000166(nucleotide binding);GO:0003774(motor activity);GO:0005516(calmodulin binding);GO:0005524(ATP binding);GO:0042803(protein homodimerization activity);GO:0051015(actin filament binding)
A_32_P820503	NM_002032	FTH1	NM_002032	Homo sapiens ferritin, heavy polypeptide 1 (FTH1), mRNA [NM_002032]	chr11	GO:0006826(iron ion transport);GO:0006879(iron ion homeostasis);GO:0006880(intracellular sequestering of iron ion);GO:0006955(immune response);GO:0008283(cell proliferation);GO:0008285(negative regulation of cell proliferation)	GO:0005886(plasma membrane);GO:0008043(ferritin complex)	GO:0004322(ferroxidase activity);GO:0005488(binding);GO:0005515(protein binding);GO:0008199(ferric iron binding);GO:0016491(oxidoreductase activity);GO:0019900(kinase binding)
A_23_P114423	NM_004683	RGN	NM_004683	Homo sapiens regucalcin (senescence marker protein-30) (RGN), transcript variant 1, mRNA [NM_004683]	chrX		GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0005509(calcium ion binding);GO:0030234(enzyme regulator activity)
A_23_P21785	NM_022072	NSUN3	NM_022072	Homo sapiens NOL1/NOP2/Sun domain family, member 3 (NSUN3), mRNA [NM_022072]	chr3			
A_32_P60145	AL834308	C1orf167	AL834308	Homo sapiens mRNA; cDNA DKFZp434F1313 (from clone DKFZp434F1313). [AL834308]	chr1			
A_23_P161257	ENST00000369797	PDCD11		RRP5 protein homolog (Programmed cell death protein 11). [Source:Uniprot/SWISSPROT;Acc:Q14690] [ENST00000369797]	chr10	GO:0006355(regulation of transcription, DNA-dependent);GO:0006364(rRNA processing);GO:0006915(apoptosis);GO:0043123(positive regulation of I-kappaB kinase/NF-kappaB cascade)	GO:0005622(intracellular);GO:0005634(nucleus);GO:0005829(cytosol)	GO:0003723(RNA binding);GO:0008134(transcription factor binding)
A_23_P110403	NM_014476	PDLIM3	NM_014476	Homo sapiens PDZ and LIM domain 3 (PDLIM3), mRNA [NM_014476]	chr4			GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P143817	NM_053025	MYLK	NM_053025	Homo sapiens myosin, light chain kinase (MYLK), transcript variant 1, mRNA [NM_053025]	chr3	GO:0006468(protein amino acid phosphorylation)		GO:0000166(nucleotide binding);GO:0000287(magnesium ion binding);GO:0004687(myosin light chain kinase activity);GO:0004871(signal transducer activity);GO:0005509(calcium ion binding);GO:0005516(calmodulin binding);GO:0005524(ATP binding);GO:0016740(transferase activity)
A_24_P29723	NM_000941	POR	NM_000941	Homo sapiens P450 (cytochrome) oxidoreductase (POR), mRNA [NM_000941]	chr7	GO:0006118(electron transport)	GO:0005625(soluble fraction);GO:0005783(endoplasmic reticulum);GO:0005792(microsome);GO:0016020(membrane)	GO:0003958(NADPH-hemoprotein reductase activity);GO:0005506(iron ion binding);GO:0009055(electron carrier activity);GO:0010181(FMN binding)
A_23_P210253	NM_152879	DGKD	NM_152879	Homo sapiens diacylglycerol kinase, delta 130kDa (DGKD), transcript variant 2, mRNA [NM_152879]	chr2	GO:0007173(epidermal growth factor receptor signaling pathway);GO:0007205(protein kinase C activation);GO:0007275(multicellular organismal development);GO:0010033(response to organic substance);GO:0016049(cell growth);GO:0019932(second-messenger-mediated signaling);GO:0046339(diacylglycerol metabolic process);GO:0051260(protein homooligomerization)	GO:0005737(cytoplasm);GO:0005886(plasma membrane)	GO:0004143(diacylglycerol kinase activity);GO:0008270(zinc ion binding);GO:0016740(transferase activity);GO:0019992(diacylglycerol binding);GO:0042803(protein homodimerization activity);GO:0046872(metal ion binding);GO:0046982(protein heterodimerization activity)
A_23_P93641	NM_020299	AKR1B10	NM_020299	Homo sapiens aldo-keto reductase family 1, member B10 (aldose reductase) (AKR1B10), mRNA [NM_020299]	chr7	GO:0006081(aldehyde metabolic process);GO:0007586(digestion);GO:0008202(steroid metabolic process)	GO:0005575(cellular_component)	GO:0004033(aldo-keto reductase activity);GO:0016491(oxidoreductase activity)
A_24_P11506	NM_003937	KYNU	NM_003937	Homo sapiens kynureninase (L-kynurenine hydrolase) (KYNU), transcript variant 1, mRNA [NM_003937]	chr2	GO:0006569(tryptophan catabolic process);GO:0008152(metabolic process);GO:0009435(NAD biosynthetic process)	GO:0005737(cytoplasm)	GO:0008233(peptidase activity);GO:0008483(transaminase activity);GO:0016787(hydrolase activity);GO:0030170(pyridoxal phosphate binding);GO:0030429(kynureninase activity)
A_23_P302005	NM_006873	STON1	NM_006873	Homo sapiens stonin 1 (STON1), mRNA [NM_006873]	chr2			

A_23_P86623	NM_020354	ENTPD7	NM_020354	Homo sapiens ectonucleoside triphosphate diphosphohydrolase 7 (ENTPD7), mRNA [NM_020354]	chr10		GO:0005773(vacuole);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005509(calcium ion binding);GO:0016787(hydrolase activity)
A_23_P132560	NM_145037	FAM55C	NM_145037	Homo sapiens family with sequence similarity 55, member C (FAM55C), mRNA [NM_145037]	chr3			
A_32_P300427	NM_153360	APCDD1L	NM_153360	Homo sapiens adenomatosis polyposis coli down-regulated 1-like (APCDD1L), mRNA [NM_153360]	chr20		GO:0016020(membrane);GO:0016021(integral to membrane)	
A_23_P206901	NM_017668	NDE1	NM_017668	Homo sapiens nudE nuclear distribution gene E homolog 1 (A. nidulans) (NDE1), mRNA [NM_017668]	chr16	GO:0007020(microtubule nucleation);GO:0007049(cell cycle);GO:0007067(mitosis);GO:0007275(multicellular organismal development);GO:0007399(nervous system development);GO:0007405(neuroblast proliferation);GO:0030154(cell differentiation);GO:0030900(forebrain development);GO:0047496(vesicle transport along microtubule);GO:0051298(centrosome duplication);GO:0051301(cell division)	GO:0005819(spindle);GO:0005856(cytoskeleton);GO:0005874(microtubule)	GO:0008017(microtubule binding);GO:0042802(identical protein binding)
A_23_P211355	NM_022720	DGCR8	NM_022720	Homo sapiens DiGeorge syndrome critical region gene 8 (DGCR8), mRNA [NM_022720]	chr22	GO:0031053(primary microRNA processing)	GO:0005622(intracellular);GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0003725(double-stranded RNA binding);GO:0005515(protein binding)
A_23_P501583	NM_002505	NFYA	NM_002505	Homo sapiens nuclear transcription factor Y, alpha (NFYA), transcript variant 1, mRNA [NM_002505]	chr6	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006366(transcription from RNA polymerase II promoter)	GO:0005634(nucleus);GO:0016602(CCAAT-binding factor complex)	GO:0003700(transcription factor activity);GO:0005515(protein binding)
A_23_P46045	NM_003617	RGS5	NM_003617	Homo sapiens regulator of G-protein signalling 5 (RGS5), mRNA [NM_003617]	chr1	GO:0008277(regulation of G-protein coupled receptor protein signaling pathway);GO:0009968(negative regulation of signal transduction)		GO:0004871(signal transducer activity);GO:0005096(GTPase activator activity)
A_32_P27271	NM_198256	E2F6	NM_198256	Homo sapiens E2F transcription factor 6 (E2F6), mRNA [NM_198256]	chr2	GO:0000074(regulation of progression through cell cycle);GO:0000122(negative regulation of transcription from RNA polymerase II promoter);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0007049(cell cycle)	GO:0005634(nucleus);GO:0005667(transcription factor complex)	GO:0003700(transcription factor activity);GO:0003714(transcription corepressor activity)
A_24_P409881	XM_291989	LOC338756	XM_291989	PREDICTED: Homo sapiens similar to nucleolar protein 5A (LOC338756), mRNA [XM_291989]	chr12			
A_23_P138635	NM_004052	BNIP3	NM_004052	Homo sapiens BCL2/adenovirus E1B 19kDa interacting protein 3 (BNIP3), nuclear gene encoding mitochondrial protein, mRNA [NM_004052]	chr10	GO:0001666(response to hypoxia);GO:0006309(DNA fragmentation during apoptosis);GO:0006338(chromatin remodeling);GO:0006800(oxygen and reactive oxygen species metabolic process);GO:0006916(anti-apoptosis);GO:0006917(induction of apoptosis);GO:0008219(cell death);GO:0008634(negative regulation of survival gene product activity);GO:0045837(negative regulation of membrane potential);GO:0046902(regulation of mitochondrial membrane permeability);GO:0051402(neuron apoptosis)	GO:0005634(nucleus);GO:0005635(nuclear envelope);GO:0005654(nucleoplasm);GO:0005737(cytoplasm);GO:0005739(mitochondrion);GO:0016020(membrane);GO:0016021(integral to membrane);GO:0030425(dendrite);GO:0031307(integral to mitochondrial outer membrane)	GO:0042803(protein homodimerization activity);GO:0046982(protein heterodimerization activity)
A_23_P252783	NM_014580	SLC2A8	NM_014580	Homo sapiens solute carrier family 2, (facilitated glucose transporter) member 8 (SLC2A8), mRNA [NM_014580]	chr9	GO:0005975(carbohydrate metabolic process);GO:0006810(transport);GO:0008643(carbohydrate transport);GO:0015758(glucose transport);GO:0015904(tetracycline transport)	GO:0005887(integral to plasma membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005215(transporter activity);GO:0005351(sugar porter activity);GO:0005355(glucose transporter activity);GO:0015520(tetracycline:hydrogen antiporter activity)
A_23_P100141	NM_023076	C16orf28	NM_023076	Homo sapiens chromosome 16 open reading frame 28 (C16orf28), mRNA [NM_023076]	chr16			GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_24_P123119	NM_001966	EHHADH	NM_001966	Homo sapiens enoyl-Coenzyme A, hydratase/3-hydroxyacyl Coenzyme A dehydrogenase (EHHADH), mRNA [NM_001966]	chr3	GO:0006091(generation of precursor metabolites and energy);GO:0006629(lipid metabolic process);GO:0006631(fatty acid metabolic process)	GO:0005739(mitochondrion);GO:0005777(peroxisome)	GO:0003857(3-hydroxyacyl-CoA dehydrogenase activity);GO:0004165(dodecenoyl-CoA delta-isomerase activity);GO:0004300(enoyl-CoA hydratase activity);GO:0016491(oxidoreductase activity);GO:0016829(lyase activity);GO:0016853(isomerase activity);GO:0050662(coenzyme binding)
A_24_P20996	BC043173	BC043173	BC043173	Homo sapiens cDNA clone IMAGE:5287121. [BC043173]	chr6			
A_32_P16931	THC2579173	THC2579173		ALU1_HUMAN (P39188) Alu subfamily J sequence contamination warning entry, partial (11%) [THC2579173]	chr2			
A_23_P130509	NM_014518	ZNF229	NM_014518	Homo sapiens zinc finger protein 229 (ZNF229), mRNA [NM_014518]	chr19	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003676(nucleic acid binding);GO:0003677(DNA binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P366328	NM_152415	VPS37A	NM_152415	Homo sapiens vacuolar protein sorting 37 homolog A (S. cerevisiae) (VPS37A), mRNA [NM_152415]	chr8			
A_23_P209636	NM_006449	CDC42EP3	NM_006449	Homo sapiens CDC42 effector protein (Rho GTPase binding) 3 (CDC42EP3), mRNA [NM_006449]	chr2	GO:0007165(signal transduction);GO:0008360(regulation of cell shape)	GO:0015629(actin cytoskeleton)	GO:0005515(protein binding);GO:0005519(cytoskeletal regulatory protein binding)
A_23_P40548	NM_013313	YPEL1	NM_013313	Homo sapiens yippee-like 1 (Drosophila) (YPEL1), mRNA [NM_013313]	chr22		GO:0005634(nucleus)	

A_23_P203115	NM_032780	TMEM25	NM_032780	Homo sapiens transmembrane protein 25 (TMEM25), mRNA [NM_032780]	chr11		GO:0016020(membrane);GO:0016021(integral to membrane)	
A_23_P78209	NM_002359	MAFG	NM_002359	Homo sapiens v-maf musculoaponeurotic fibrosarcoma oncogene homolog G (avian) (MAFG), transcript variant 1, mRNA [NM_002359]	chr17	GO:0001701(in utero embryonic development);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006366(transcription from RNA polymerase II promoter);GO:0030534(adult behavior);GO:0042127(regulation of cell proliferation);GO:0045604(regulation of epidermal cell differentiation)	GO:0000785(chromatin);GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0046983(protein dimerization activity)
A_24_P451992	XR_018393	LOC342705	XR_018393	PREDICTED: Homo sapiens similar to 6-phosphogluconate dehydrogenase, decarboxylating (LOC342705), mRNA [XR_018393]	chr18			
A_32_P226858	THC2557016	THC2557016		Q3F710_9BURK (Q3F710) Inner-membrane translocator, partial (6%) [THC2557016]	chr1			
A_23_P63459	NM_001012985	C1orf31	NM_001012985	Homo sapiens chromosome 1 open reading frame 31 (C1orf31), mRNA [NM_001012985]	chr1	GO:0006118(electron transport)	GO:0005739(mitochondrion)	GO:0004129(cytochrome-c oxidase activity)
A_32_P82293	A_32_P82293	A_32_P82293			chr6			
A_23_P33511	AX721087	AX721087	AX721087	Sequence 47 from Patent WO0220754. [AX721087]	chr8			
A_23_P311912	BC090889	AHNAK2	BC090889	Homo sapiens AHNAK nucleoprotein 2, mRNA (cDNA clone MGC:102983 IMAGE:30387958), complete cds. [BC090889]	chr14			GO:0005515(protein binding)
A_23_P250102	NM_012298	CAND2	NM_012298	Homo sapiens cullin-associated and neddylation-dissociated 2 (putative) (CAND2), mRNA [NM_012298]	chr3	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006512(ubiquitin cycle)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0016563(transcriptional activator activity);GO:0017025(TATA-binding protein binding)
A_24_P298179	A_24_P298179	A_24_P298179			chr9			
A_32_P13823	THC2719076	THC2719076			chr3			
A_24_P167063	NM_014803	ZNF518	NM_014803	Homo sapiens zinc finger protein 518 (ZNF518), mRNA [NM_014803]	chr10	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_32_P190316	THC2645336	THC2645336			chr6			
A_23_P500130	NM_153186	ANKRD15	NM_153186	Homo sapiens ankyrin repeat domain 15 (ANKRD15), transcript variant 2, mRNA [NM_153186]	chr9	GO:0007049(cell cycle);GO:0045786(negative regulation of progression through cell cycle)		
A_24_P152845	XR_018726	LOC340888	XR_018726	PREDICTED: Homo sapiens similar to aldo-keto reductase family 1, member B10 (LOC340888), mRNA [XR_018726]	chr10			
A_32_P188860	NM_017563	IL17RD	NM_017563	Homo sapiens interleukin 17 receptor D (IL17RD), transcript variant 2, mRNA [NM_017563]	chr3		GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0004888(transmembrane receptor activity)
A_32_P112078	THC2538534	THC2538534			chr7			
A_24_P148261	ENST00000366930	TGFB2		Transforming growth factor beta-2 precursor (TGF-beta-2) (Glioblastoma-derived T-cell suppressor factor) (G-TSF) (BSC-1 cell growth inhibitor) (Polyergin) (Cetermin). [Source:Uniprot/SWISSPROT;Acc:P61812] [ENST00000366930]	chr1	GO:0000902(cell morphogenesis);GO:0001501(skeletal development);GO:0001525(angiogenesis);GO:0001568(blood vessel development);GO:0001654(eye development);GO:0001707(mesoderm formation);GO:0001837(epithelial to mesenchymal transition);GO:0001942(hair follicle development);GO:0007267(cell-cell signaling);GO:0007411(axon guidance);GO:0007507(heart development);GO:0008219(cell death);GO:0008283(cell proliferation);GO:0008284(positive regulation of cell proliferation);GO:0008285(negative regulation of cell proliferation);GO:0009790(embryonic development);GO:0010002(cardioblast differentiation);GO:0016049(cell growth);GO:0030097(hemopoiesis);GO:0030198(extracellular matrix organization and biogenesis);GO:0030307(positive regulation of cell growth);GO:0030593(neutrophil chemotaxis);GO:0031069(hair follicle morphogenesis);GO:0042060(wound healing);GO:0042416(dopamine biosynthetic process);GO:0042637(catagen);GO:0042981(regulation of apoptosis);GO:0045617(negative regulation of keratinocyte differentiation);GO:0045787(positive regulation of progression through cell cycle);GO:0045823(positive regulation of heart contraction);GO:0048103(somatic stem cell division);GO:0050777(negative regulation of immune response);GO:0050778(positive regulation of immune response)	GO:0005576(extracellular region);GO:0030424(axon);GO:0043025(cell soma)	GO:0001540(beta-amyloid binding);GO:0005125(cytokine activity);GO:0005160(transforming growth factor beta receptor binding);GO:0005515(protein binding);GO:0008083(growth factor activity);GO:0042803(protein homodimerization activity);GO:0046982(protein heterodimerization activity)
A_23_P70748	NM_031922	REPS1	NM_031922	Homo sapiens RALBP1 associated Eps domain containing 1 (REPS1), mRNA [NM_031922]	chr6			GO:0005509(calcium ion binding);GO:0005515(protein binding)
A_23_P159125	NM_004695	SLC16A5	NM_004695	Homo sapiens solute carrier family 16, member 5 (monocarboxylic acid transporter 6) (SLC16A5), mRNA [NM_004695]	chr17	GO:0006810(transport);GO:0015711(organic anion transport);GO:0015718(monocarboxylic acid transport)	GO:0005624(membrane fraction);GO:0005887(integral to plasma membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005215(transporter activity);GO:0015293(symporter activity);GO:0015355(monocarboxylate porter activity)
A_23_P337729	NM_024789	TMEM180	NM_024789	Homo sapiens transmembrane protein 180 (TMEM180), mRNA [NM_024789]	chr10		GO:0016020(membrane);GO:0016021(integral to membrane)	

A_23_P208551	NM_001008701	LPHN1	NM_001008701	Homo sapiens latrophilin 1 (LPHN1), transcript variant 1, mRNA [NM_001008701]	chr19	GO:0007165(signal transduction);GO:0007218(neuropeptide signaling pathway)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0004872(receptor activity);GO:0004930(G-protein coupled receptor activity);GO:0005529(sugar binding);GO:0016524(latrotoxin receptor activity)
A_23_P8834	NM_001979	EPHX2	NM_001979	Homo sapiens epoxide hydrolase 2, cytoplasmic (EPHX2), mRNA [NM_001979]	chr8	GO:0006800(oxygen and reactive oxygen species metabolic process);GO:0006805(xenobiotic metabolic process);GO:0006874(calcium ion homeostasis);GO:0006954(inflammatory response);GO:0008152(metabolic process);GO:0008217(blood pressure regulation);GO:0009636(response to toxin);GO:0017144(drug metabolic process);GO:0019439(aromatic compound catabolic process);GO:0045909(positive regulation of vasodilation)	GO:0005625(soluble fraction);GO:0005777(peroxisome);GO:0005829(cytosol)	GO:0000287(magnesium ion binding);GO:0004301(epoxide hydrolase activity);GO:0016787(hydrolase activity);GO:0042803(protein homodimerization activity)
A_23_P103996	NM_002061	GCLM	NM_002061	Homo sapiens glutamate-cysteine ligase, modifier subunit (GCLM), mRNA [NM_002061]	chr1	GO:0006534(cysteine metabolic process);GO:0006536(glutamate metabolic process);GO:0006750(glutathione biosynthetic process);GO:0006979(response to oxidative stress);GO:0035229(positive regulation of glutamate-cysteine ligase activity);GO:0042493(response to drug);GO:0050880(regulation of blood vessel size)	GO:0005625(soluble fraction);GO:0005829(cytosol);GO:0017109(glutamate-cysteine ligase complex)	GO:0004357(glutamate-cysteine ligase activity);GO:0005515(protein binding);GO:0016491(oxidoreductase activity);GO:0016874(ligase activity);GO:0035226(glutamate-cysteine ligase catalytic subunit binding);GO:0046982(protein heterodimerization activity)
A_32_P165477	NM_014331	SLC7A11	NM_014331	Homo sapiens solute carrier family 7, (cationic amino acid transporter, y+ system) member 11 (SLC7A11), mRNA [NM_014331]	chr4	GO:0006461(protein complex assembly);GO:0006810(transport);GO:0006865(amino acid transport)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0015171(amino acid transporter activity);GO:0015327(cystine:glutamate antiporter activity);GO:0015359(amino acid permease activity)
A_23_P158976	NM_000392	ABCC2	NM_000392	Homo sapiens ATP-binding cassette, sub-family C (CFTR/MRP), member 2 (ABCC2), mRNA [NM_000392]	chr10	GO:0006810(transport)	GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0000166(nucleotide binding);GO:0005215(transporter activity);GO:0005524(ATP binding);GO:0008514(organic anion transporter activity);GO:0016887(ATPase activity);GO:0042626(ATPase activity, coupled to transmembrane movement of substances)
A_24_P860797	ENST00000244221	PAIP2B		Homo sapiens cDNA FLJ37016 fis, clone BRACE2010632. [AK094335]	chr2			
A_23_P120931	NM_014508	APOBEC3C	NM_014508	Homo sapiens apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3C (APOBEC3C), mRNA [NM_014508]	chr22	GO:0008150(biological_process)	GO:0005575(cellular_component)	GO:0003674(molecular_function);GO:0003723(RNA binding);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0016787(hydrolase activity);GO:0016814(hydrolase activity, acting on carbon-nitrogen (but not peptide) bonds, in cyclic amidines);GO:0046872(metal ion binding)
A_24_P347566	NM_015059	TLN2	NM_015059	Homo sapiens talin 2 (TLN2), mRNA [NM_015059]	chr15	GO:0007016(cytoskeletal anchoring);GO:0007043(intercellular junction assembly);GO:0007155(cell adhesion)	GO:0001726(ruffle);GO:0005911(intercellular junction);GO:0005925(focal adhesion);GO:0015629(actin cytoskeleton);GO:0045202(synapse)	GO:0003779(actin binding);GO:0005200(structural constituent of cytoskeleton);GO:0005515(protein binding)
A_23_P308800	AF158555	GLS	AF158555	Homo sapiens glutaminase C mRNA, complete cds. [AF158555]	chr2	GO:0006543(glutamine catabolic process)	GO:0005739(mitochondrion)	GO:0004359(glutaminase activity);GO:0016787(hydrolase activity)
A_24_P163237	NM_020225	STOX2	NM_020225	Homo sapiens storkhead box 2 (STOX2), mRNA [NM_020225]	chr4			
A_23_P86079	M32220	M32220	M32220	Human DNA/endogenous retroviral long terminal repeat (LTR) junction mRNA, clone lambda-LTR22. [M32220]	chr1			
A_23_P501822	NM_002230	JUP	NM_002230	Homo sapiens junction plakoglobin (JUP), transcript variant 1, mRNA [NM_002230]	chr17	GO:0007155(cell adhesion);GO:0016055(Wnt receptor signaling pathway)	GO:0005624(membrane fraction);GO:0005625(soluble fraction);GO:0005737(cytoplasm);GO:0005829(cytosol);GO:0005856(cytoskeleton);GO:0005913(cell-cell adherens junction);GO:0030057(desmosome)	GO:0005198(structural molecule activity);GO:0005488(binding);GO:0008092(cytoskeletal protein binding)
A_23_P216023	NM_001146	ANGPT1	NM_001146	Homo sapiens angiopoietin 1 (ANGPT1), mRNA [NM_001146]	chr8	GO:0001525(angiogenesis);GO:0007165(signal transduction);GO:0007169(transmembrane receptor protein tyrosine kinase signaling pathway);GO:0007275(multicellular organismal development);GO:0030154(cell differentiation)		GO:0005102(receptor binding)
A_23_P112481	NM_004925	AQP3	NM_004925	Homo sapiens aquaporin 3 (Gill blood group) (AQP3), mRNA [NM_004925]	chr9	GO:0006810(transport);GO:0007588(excretion)	GO:0005624(membrane fraction);GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0005215(transporter activity)
A_23_P143374	NM_025176	RP4-691N24.1	NM_025176	Homo sapiens KIAA0980 protein (KIAA0980), mRNA [NM_025176]	chr20		GO:0005874(microtubule)	GO:0005509(calcium ion binding)
A_32_P108156	NR_001458	BIC	NR_001458	Homo sapiens BIC transcript (BIC) on chromosome 21 [NR_001458]	chr21			
A_23_P316601	NM_006912	RIT1	NM_006912	Homo sapiens Ras-like without CAAX 1 (RIT1), mRNA [NM_006912]	chr1	GO:0007165(signal transduction);GO:0007264(small GTPase mediated signal transduction)	GO:0005622(intracellular);GO:0005886(plasma membrane);GO:0016020(membrane)	GO:0000166(nucleotide binding);GO:0005516(calmodulin binding);GO:0005525(GTP binding)
A_32_P135336	NR_002556	LOC388242	NR_002556	Homo sapiens LOC112869 pseudogene (LOC388242) on chromosome 16 [NR_002556]	chr16			
A_23_P62159	BC016138	FAM120C	BC016138	Homo sapiens family with sequence similarity 120C, mRNA (cDNA clone IMAGE:3921622), complete cds. [BC016138]	chrX			
A_32_P497742	AK091271	GPR161	AK091271	Homo sapiens cDNA FLJ33952 fis, clone CTONG2018614. [AK091271]	chr1	GO:0007165(signal transduction);GO:0007186(G-protein coupled receptor protein signaling pathway)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0001584(rhodopsin-like receptor activity);GO:0004872(receptor activity)

A_23_P155162	NM_052839	PANX2	NM_052839	Homo sapiens pannexin 2 (PANX2), mRNA [NM_052839]	chr22		GO:0005921(gap junction);GO:0016020(membrane);GO:0016021(integral to membrane)	
A_24_P340390	NM_182485	CPEB2	NM_182485	Homo sapiens cytoplasmic polyadenylation element binding protein 2 (CPEB2), transcript variant B, mRNA [NM_182485]	chr4	GO:0006417(regulation of translation)		GO:0000166(nucleotide binding);GO:0003723(RNA binding)
A_23_P253012	NM_017577	GRAMD1C	NM_017577	Homo sapiens GRAM domain containing 1C (GRAMD1C), mRNA [NM_017577]	chr3			
A_24_P354651	NM_153354	TMEM161B	NM_153354	Homo sapiens transmembrane protein 161B (TMEM161B), mRNA [NM_153354]	chr5		GO:0016021(integral to membrane)	
A_23_P151426	NM_002015	FOXO1	NM_002015	Homo sapiens forkhead box O1A (FOXO1A), mRNA [NM_002015]	chr13	GO:0001568(blood vessel development);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006916(anti-apoptosis);GO:0008286(insulin receptor signaling pathway);GO:0042127(regulation of cell proliferation);GO:0045944(positive regulation of transcription from RNA polymerase II promoter)	GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0003700(transcription factor activity);GO:0005515(protein binding);GO:0016563(transcriptional activator activity)
A_23_P125233	NM_001299	CNN1	NM_001299	Homo sapiens calponin 1, basic, smooth muscle (CNN1), mRNA [NM_001299]	chr19	GO:0006940(regulation of smooth muscle contraction);GO:0031032(actomyosin structure organization and biogenesis)		GO:0003779(actin binding);GO:0005516(calmodulin binding)
A_23_P125788	NM_152278	TCEAL7	NM_152278	Homo sapiens transcription elongation factor A (SII)-like 7 (TCEAL7), mRNA [NM_152278]	chrX	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0008150(biological_process)	GO:0005575(cellular_component);GO:0005634(nucleus)	GO:0003674(molecular_function)
A_23_P91390	NM_000361	THBD	NM_000361	Homo sapiens thrombomodulin (THBD), mRNA [NM_000361]	chr20	GO:0007565(pregnancy);GO:0007596(blood coagulation);GO:0009790(embryonic development)	GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0004888(transmembrane receptor activity);GO:0005509(calcium ion binding);GO:0005515(protein binding);GO:0005529(sugar binding)
A_23_P70409	NM_004875	POLR1C	NM_004875	Homo sapiens polymerase (RNA) I polypeptide C, 30kDa (POLR1C), transcript variant 2, mRNA [NM_004875]	chr6	GO:0006350(transcription);GO:0006360(transcription from RNA polymerase I promoter)	GO:0005634(nucleus);GO:0005736(DNA-directed RNA polymerase I complex)	GO:0003677(DNA binding);GO:0003899(DNA-directed RNA polymerase activity);GO:0016740(transferase activity);GO:0046983(protein dimerization activity)
A_23_P5441	NM_005689	ABCB6	NM_005689	Homo sapiens ATP-binding cassette, sub-family B (MDR/TAP), member 6 (ABCB6), nuclear gene encoding mitochondrial protein, mRNA [NM_005689]	chr2	GO:0006810(transport);GO:0006879(iron ion homeostasis)	GO:0005739(mitochondrion);GO:0005740(mitochondrial envelope);GO:0016020(membrane);GO:0016021(integral to membrane);GO:0019867(outer membrane);GO:0043190(ATP-binding cassette (ABC) transporter complex)	GO:0000166(nucleotide binding);GO:0005524(ATP binding);GO:0016887(ATPase activity);GO:0042626(ATPase activity, coupled to transmembrane movement of substances)
A_23_P90357	NM_201636	TBXA2R	NM_201636	Homo sapiens thromboxane A2 receptor (TBXA2R), transcript variant 1, mRNA [NM_201636]	chr19	GO:0006936(muscle contraction);GO:0007165(signal transduction);GO:0007186(G-protein coupled receptor protein signaling pathway);GO:0007585(respiratory gaseous exchange)	GO:0005886(plasma membrane);GO:0005887(integral to plasma membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0001584(rhodopsin-like receptor activity);GO:0004872(receptor activity);GO:0004960(thromboxane receptor activity);GO:0004961(thromboxane A2 receptor activity)
A_23_P156101	NM_002270	TNPO1	NM_002270	Homo sapiens transportin 1 (TNPO1), transcript variant 1, mRNA [NM_002270]	chr5	GO:0000059(protein import into nucleus, docking);GO:0000060(protein import into nucleus, translocation);GO:0006886(intracellular protein transport)	GO:0005634(nucleus);GO:0005643(nuclear pore);GO:0005737(cytoplasm)	GO:0005515(protein binding);GO:0008139(nuclear localization sequence binding);GO:0008565(protein transporter activity)
A_23_P69226	NM_018447	TMEM111	NM_018447	Homo sapiens transmembrane protein 111 (TMEM111), mRNA [NM_018447]	chr3		GO:0016020(membrane);GO:0016021(integral to membrane)	
A_24_P278167	NM_006007	ZFAND5	NM_006007	Homo sapiens zinc finger, AN1-type domain 5 (ZFAND5), mRNA [NM_006007]	chr9	GO:0008150(biological_process)	GO:0005575(cellular_component)	GO:0003674(molecular_function);GO:0003677(DNA binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_24_P755069	A_24_P755069	A_24_P755069			chr9			
A_32_P146815	BC062473	BC062473	BC062473	Homo sapiens cDNA clone IMAGE:30374677, partial cds. [BC062473]	chr12			
A_23_P29655	NM_020685	C3orf14	NM_020685	Homo sapiens chromosome 3 open reading frame 14 (C3orf14), mRNA [NM_020685]	chr3			
A_23_P126623	NM_002631	PGD	NM_002631	Homo sapiens phosphogluconate dehydrogenase (PGD), mRNA [NM_002631]	chr1	GO:0006118(electron transport);GO:0009051(pentose-phosphate shunt, oxidative branch)		GO:0004616(phosphogluconate dehydrogenase (decarboxylating) activity);GO:0005515(protein binding);GO:0016491(oxidoreductase activity);GO:0050661(NADP binding)
A_23_P82047	BU507302	BU507302	BU507302	AGENCOURT_10309688 NIH_MGC_71 Homo sapiens cDNA clone IMAGE:6501220 5', mRNA sequence [BU507302]	chr6			
A_23_P202104	NM_005729	PPIF	NM_005729	Homo sapiens peptidylprolyl isomerase F (cyclophilin F) (PPIF), nuclear gene encoding mitochondrial protein, mRNA [NM_005729]	chr10	GO:0006457(protein folding)	GO:0005624(membrane fraction);GO:0005739(mitochondrion)	GO:0003755(peptidyl-prolyl cis-trans isomerase activity);GO:0016853(isomerase activity);GO:0042277(peptide binding)
A_23_P75220	NM_031212	SLC25A28	NM_031212	Homo sapiens solute carrier family 25, member 28 (SLC25A28), mRNA [NM_031212]	chr10	GO:0006811(ion transport);GO:0006826(iron ion transport)	GO:0005739(mitochondrion);GO:0005743(mitochondrial inner membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005488(binding);GO:0005506(iron ion binding)
A_32_P88479	NM_015264	C22orf9	NM_015264	Homo sapiens chromosome 22 open reading frame 9 (C22orf9), transcript variant 1, mRNA [NM_015264]	chr22			GO:0005515(protein binding)
A_32_P226646	THC2661917	THC2661917			chr16			
A_23_P345674	NM_021216	ZNF71	NM_021216	Homo sapiens zinc finger protein 71 (ZNF71), mRNA [NM_021216]	chr19	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)

A_32_P79396	NM_005746	PBEF1	NM_005746	Homo sapiens pre-B-cell colony enhancing factor 1 (PBEF1), mRNA [NM_005746]	chr7	GO:0007165(signal transduction);GO:0007267(cell-cell signaling);GO:0008284(positive regulation of cell proliferation);GO:0019363(pyridine nucleotide biosynthetic process)		GO:0004516(nicotinate phosphoribosyltransferase activity);GO:0005125(cytokine activity);GO:0016757(transferase activity, transferring glycosyl groups);GO:0047280(nicotinamide phosphoribosyltransferase activity)
A_23_P83931	NM_005863	NET1	NM_005863	Homo sapiens neuroepithelial cell transforming gene 1 (NET1), transcript variant 2, mRNA [NM_005863]	chr10	GO:0001558(regulation of cell growth);GO:0007165(signal transduction);GO:0035023(regulation of Rho protein signal transduction)	GO:0005575(cellular_component);GO:0005622(intracellular);GO:0005634(nucleus)	GO:0005085(guanyl-nucleotide exchange factor activity);GO:0005089(Rho guanyl-nucleotide exchange factor activity)
A_23_P205519	NM_022060	ABHD4	NM_022060	Homo sapiens abhydrolase domain containing 4 (ABHD4), mRNA [NM_022060]	chr14	GO:0006508(proteolysis);GO:0006725(aromatic compound metabolic process);GO:0016042(lipid catabolic process)		GO:0004177(aminopeptidase activity);GO:0016787(hydrolase activity)
A_24_P54670	NM_003043	SLC6A6	NM_003043	Homo sapiens solute carrier family 6 (neurotransmitter transporter, taurine), member 6 (SLC6A6), mRNA [NM_003043]	chr3	GO:0001762(beta-alanine transport);GO:0006520(amino acid metabolic process);GO:0006836(neurotransmitter transport);GO:0015734(taurine transport)	GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0001761(beta-alanine transporter activity);GO:0005369(taurine:sodium symporter activity);GO:0015293(symporter activity)
A_24_P93741	AK098811	LOC285398	AK098811	Homo sapiens cDNA FLJ25945 fis, clone JTH12731. [AK098811]	chr3			
A_23_P91350	ENST00000379019	RP5-1022P6.2		Putative glycerophosphodiester phosphodiesterase 5 (EC 3.1.-.-). [Source:Uniprot/SWISSPROT;Acc:Q9NPB8] [ENST00000379019]	chr20	GO:0005975(carbohydrate metabolic process);GO:0006071(glycerol metabolic process)		GO:0008889(glycerophosphodiester phosphodiesterase activity);GO:0016787(hydrolase activity);GO:0030246(carbohydrate binding)
A_24_P945113	NM_000020	ACVRL1	NM_000020	Homo sapiens activin A receptor type II-like 1 (ACVRL1), transcript variant 1, mRNA [NM_000020]	chr12	GO:0001525(angiogenesis);GO:0006468(protein amino acid phosphorylation);GO:0007162(negative regulation of cell adhesion);GO:0007165(signal transduction);GO:0007179(transforming growth factor beta receptor signaling pathway);GO:0008217(blood pressure regulation);GO:0008285(negative regulation of cell proliferation);GO:0030336(negative regulation of cell migration);GO:0035313(wound healing, spreading of epidermal cells);GO:0045941(positive regulation of transcription)	GO:0005887(integral to plasma membrane);GO:0009986(cell surface);GO:0016020(membrane)	GO:0000166(nucleotide binding);GO:0000287(magnesium ion binding);GO:0004872(receptor activity);GO:0005524(ATP binding);GO:0016361(activin receptor activity, type I);GO:0016740(transferase activity);GO:0030145(manganese ion binding);GO:0046332(SMAD binding);GO:0048185(activin binding);GO:0050431(transforming growth factor beta binding)
A_32_P224727	BE798911	BE798911	BE798911	601585434F1 NIH_MGC_7 Homo sapiens cDNA clone IMAGE:3939776 5', mRNA sequence [BE798911]	chr2			
A_32_P206949	NM_198276	TMEM17	NM_198276	Homo sapiens transmembrane protein 17 (TMEM17), mRNA [NM_198276]	chr2		GO:0016020(membrane);GO:0016021(integral to membrane)	
A_24_P252364	NM_005010	NRCAM	NM_005010	Homo sapiens neuronal cell adhesion molecule (NRCAM), transcript variant 2, mRNA [NM_005010]	chr7	GO:0001764(neuron migration);GO:0007413(axonal fasciculation);GO:0007416(synaptogenesis);GO:0007417(central nervous system development);GO:0016337(cell-cell adhesion);GO:0030516(regulation of axon extension);GO:0045162(clustering of voltage-gated sodium channels);GO:0045666(positive regulation of neuron differentiation)	GO:0005887(integral to plasma membrane);GO:0009897(external side of plasma membrane);GO:0016020(membrane);GO:0043005(neuron projection)	GO:0005515(protein binding);GO:0030506(ankyrin binding)
A_23_P170626	NM_001011667	CHCHD7	NM_001011667	Homo sapiens coiled-coil-helix-coiled-coil-helix domain containing 7 (CHCHD7), transcript variant 1, mRNA [NM_001011667]	chr8			
A_23_P78053	NM_030802	FAM117A	NM_030802	Homo sapiens family with sequence similarity 117, member A (FAM117A), mRNA [NM_030802]	chr17			
A_23_P23855	NM_032305	POLR3GL	NM_032305	Homo sapiens polymerase (RNA) III (DNA directed) polypeptide G (32kD)-like (POLR3GL), mRNA [NM_032305]	chr1			
A_23_P77048	NM_152333	SLC25A29	NM_152333	Homo sapiens solute carrier family 25, member 29 (SLC25A29), transcript variant 2, mRNA [NM_152333]	chr14	GO:0006810(transport)	GO:0005739(mitochondrion);GO:0005743(mitochondrial inner membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005215(transporter activity);GO:0005488(binding)
A_24_P152188	NM_198859	PRICKLE2	NM_198859	Homo sapiens prickle homolog 2 (Drosophila) (PRICKLE2), mRNA [NM_198859]	chr3		GO:0005634(nucleus);GO:0005737(cytoplasm);GO:0016020(membrane)	GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P90419	NM_025245	PBX4	NM_025245	Homo sapiens pre-B-cell leukemia homeobox 4 (PBX4), mRNA [NM_025245]	chr19	GO:0006355(regulation of transcription, DNA-dependent);GO:0009790(embryonic development);GO:0030902(hindbrain development);GO:0045898(regulation of transcriptional preinitiation complex formation)	GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0005515(protein binding)
A_23_P258190	NM_001628	AKR1B1	NM_001628	Homo sapiens aldo-keto reductase family 1, member B1 (aldose reductase) (AKR1B1), mRNA [NM_001628]	chr7	GO:0005975(carbohydrate metabolic process);GO:0006950(response to stress)	GO:0005615(extracellular space)	GO:0004032(aldehyde reductase activity);GO:0005515(protein binding);GO:0009055(electron carrier activity);GO:0016491(oxidoreductase activity)
A_23_P67198	NM_015692	CPAMD8	NM_015692	Homo sapiens C3 and PZP-like, alpha-2-macroglobulin domain containing 8 (CPAMD8), mRNA [NM_015692]	chr19			GO:0004866(endopeptidase inhibitor activity)
A_23_P206598	THC2726281	THC2726281		P97868_MOUSE (P97868) Proliferation potential-related protein, partial (4%) [THC2726281]	chr16			
A_23_P35414	NM_005398	PPP1R3C	NM_005398	Homo sapiens protein phosphatase 1, regulatory (inhibitor) subunit 3C (PPP1R3C), mRNA [NM_005398]	chr10			GO:0000163(protein phosphatase type 1 activity)

A_23_P46351	NM_006862	TDRKH	NM_006862	Homo sapiens tudor and KH domain containing (TDRKH), mRNA [NM_006862]	chr1		GO:0016020(membrane)	GO:0003723(RNA binding)
A_23_P7896	NM_020185	DUSP22	NM_020185	Homo sapiens dual specificity phosphatase 22 (DUSP22), mRNA [NM_020185]	chr6	GO:0000188(inactivation of MAPK activity);GO:0006470(protein amino acid dephosphorylation);GO:0006915(apoptosis);GO:0007179(transforming growth factor beta receptor signaling pathway);GO:0007275(multicellular organismal development);GO:0042127(regulation of cell proliferation);GO:0046330(positive regulation of JNK cascade)	GO:0005634(nucleus)	GO:0004725(protein tyrosine phosphatase activity);GO:0005515(protein binding);GO:0008138(protein tyrosine/serine/threonine phosphatase activity);GO:0016787(hydrolase activity)
A_24_P258073	NM_021830	PEO1	NM_021830	Homo sapiens progressive external ophthalmoplegia 1 (PEO1), mRNA [NM_021830]	chr10	GO:0006260(DNA replication)	GO:0005739(mitochondrion)	GO:0000166(nucleotide binding);GO:0003678(DNA helicase activity);GO:0005524(ATP binding);GO:0016787(hydrolase activity)
A_23_P200073	NM_020362	C1orf128	NM_020362	Homo sapiens chromosome 1 open reading frame 128 (C1orf128), mRNA [NM_020362]	chr1			
A_23_P65983	NM_033212	CCDC102A	NM_033212	Homo sapiens coiled-coil domain containing 102A (CCDC102A), mRNA [NM_033212]	chr16			
A_23_P419947	NM_022443	MLF1	NM_022443	Homo sapiens myeloid leukemia factor 1 (MLF1), mRNA [NM_022443]	chr3	GO:0006350(transcription);GO:0007050(cell cycle arrest);GO:0007275(multicellular organismal development);GO:0030154(cell differentiation)	GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0003677(DNA binding);GO:0005515(protein binding);GO:0019904(protein domain specific binding)
A_24_P309594	BC026344	FLJ20489	BC026344	Homo sapiens hypothetical protein FLJ20489, mRNA (cDNA clone MGC:26667 IMAGE:4798578), complete cds. [BC026344]	chr12			
A_24_P919850	NM_000710	BDKRB1	NM_000710	Homo sapiens bradykinin receptor B1 (BDKRB1), mRNA [NM_000710]	chr14	GO:0006954(inflammatory response);GO:0007165(signal transduction);GO:0007186(G-protein coupled receptor protein signaling pathway);GO:0007204(elevation of cytosolic calcium ion concentration)	GO:0005783(endoplasmic reticulum);GO:0005886(plasma membrane);GO:0005887(integral to plasma membrane)	GO:0001584(rhodopsin-like receptor activity);GO:0004872(receptor activity);GO:0004947(bradykinin receptor activity)
A_23_P253932	NM_018147	FAIM	NM_018147	Homo sapiens Fas apoptotic inhibitory molecule (FAIM), transcript variant 4, mRNA [NM_018147]	chr3	GO:0006915(apoptosis);GO:0006916(anti-apoptosis);GO:0043066(negative regulation of apoptosis)		
A_23_P50504	NM_000146	FTL	NM_000146	Homo sapiens ferritin, light polypeptide (FTL), mRNA [NM_000146]	chr19	GO:0006826(iron ion transport);GO:0006879(iron ion homeostasis)	GO:0008043(ferritin complex)	GO:0005488(binding);GO:0008199(ferric iron binding);GO:0016491(oxidoreductase activity);GO:0042802(identical protein binding)
A_23_P150807	NM_003621	PPFIBP2	NM_003621	Homo sapiens PTPRF interacting protein, binding protein 2 (liprin beta 2) (PPFIBP2), mRNA [NM_003621]	chr11	GO:0007154(cell communication)	GO:0005622(intracellular)	GO:0003674(molecular_function)
A_23_P129005	NM_025081	KIAA1305	NM_025081	Homo sapiens KIAA1305 (KIAA1305), mRNA [NM_025081]	chr14	GO:0015074(DNA integration)		GO:0003677(DNA binding)
A_23_P11995	NM_002574	PRDX1	NM_002574	Homo sapiens peroxiredoxin 1 (PRDX1), transcript variant 1, mRNA [NM_002574]	chr1	GO:0001501(skeletal development);GO:0008283(cell proliferation)		GO:0016491(oxidoreductase activity)
A_23_P160546	NM_018379	FAM63A	NM_018379	Homo sapiens family with sequence similarity 63, member A (FAM63A), transcript variant 1, mRNA [NM_018379]	chr1			GO:0005515(protein binding)
A_23_P99582	NM_002687	PNN	NM_002687	Homo sapiens pinin, desmosome associated protein (PNN), mRNA [NM_002687]	chr14	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006397(mRNA processing);GO:0007049(cell cycle);GO:0007155(cell adhesion);GO:0008380(RNA splicing);GO:0045786(negative regulation of progression through cell cycle)	GO:0005634(nucleus);GO:0005681(spliceosome);GO:0005737(cytoplasm);GO:0005882(intermediate filament);GO:0005886(plasma membrane);GO:0005911(intercellular junction);GO:0016607(nuclear speck)	GO:0003677(DNA binding);GO:0005198(structural molecule activity);GO:0005515(protein binding)
A_23_P426021	NM_015187	KIAA0746	NM_015187	Homo sapiens KIAA0746 protein (KIAA0746), mRNA [NM_015187]	chr4			GO:0005488(binding)
A_23_P376449	XR_016155	LOC642413	XR_016155	PREDICTED: Homo sapiens similar to Cathepsin L precursor (Major excreted protein) (MEP) (LOC642413), mRNA [XR_016155]	chr10			
A_23_P6771	NM_014583	LMCD1	NM_014583	Homo sapiens LIM and cysteine-rich domains 1 (LMCD1), mRNA [NM_014583]	chr3	GO:0000122(negative regulation of transcription from RNA polymerase II promoter);GO:0008150(biological_process)	GO:0005575(cellular_component);GO:0005634(nucleus)	GO:0003674(molecular_function);GO:0003714(transcription corepressor activity);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P117146	NM_012406	PRDM4	NM_012406	Homo sapiens PR domain containing 4 (PRDM4), mRNA [NM_012406]	chr12	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006366(transcription from RNA polymerase II promoter);GO:0007165(signal transduction);GO:0008283(cell proliferation)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0003702(RNA polymerase II transcription factor activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P143885	NM_019555	ARHGEF3	NM_019555	Homo sapiens Rho guanine nucleotide exchange factor (GEF) 3 (ARHGEF3), mRNA [NM_019555]	chr3	GO:0035023(regulation of Rho protein signal transduction)	GO:0005622(intracellular)	GO:0005085(guanyl-nucleotide exchange factor activity);GO:0005089(Rho guanyl-nucleotide exchange factor activity)
A_23_P148410	NM_031894	FTHL17	NM_031894	Homo sapiens ferritin, heavy polypeptide-like 17 (FTHL17), mRNA [NM_031894]	chrX	GO:0006826(iron ion transport);GO:0006879(iron ion homeostasis)		GO:0005488(binding);GO:0008199(ferric iron binding);GO:0016491(oxidoreductase activity)
A_23_P44083	NM_002056	GFPT1	NM_002056	Homo sapiens glutamine-fructose-6-phosphate transaminase 1 (GFPT1), mRNA [NM_002056]	chr2	GO:0006002(fructose 6-phosphate metabolic process);GO:0006112(energy reserve metabolic process);GO:0006541(glutamine metabolic process);GO:0008152(metabolic process);GO:0016051(carbohydrate biosynthetic process)	GO:0005737(cytoplasm)	GO:0004360(glutamine-fructose-6-phosphate transaminase (isomerizing) activity);GO:0005529(sugar binding);GO:0016740(transferase activity)

A_23_P217958	NM_033500	HK1	NM_033500	Homo sapiens hexokinase 1 (HK1), nuclear gene encoding mitochondrial protein, transcript variant 5, mRNA [NM_033500]	chr10	GO:0006096(glycolysis)	GO:0016020(membrane)	GO:0000166(nucleotide binding);GO:0004396(hexokinase activity);GO:0005524(ATP binding);GO:0016301(kinase activity);GO:0016740(transferase activity)
A_32_P212886	BC014117	TBXAS1	BC014117	Homo sapiens thromboxane A synthase 1 (platelet, cytochrome P450, family 5, subfamily A), mRNA (cDNA clone MGC:20885 IMAGE:4548935), complete cds. [BC014117]	chr7	GO:0001516(prostaglandin biosynthetic process);GO:0006118(electron transport);GO:0006633(fatty acid biosynthetic process);GO:0007596(blood coagulation)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0004796(thromboxane-A synthase activity);GO:0005506(iron ion binding);GO:0016712(oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, reduced flavin or flavoprotein as one donor, and incorporation of one atom of oxygen);GO:0016853(isomerase activity);GO:0020037(heme binding);GO:0046872(metal ion binding)
A_23_P61987	NM_025268	TMEM121	NM_025268	Homo sapiens transmembrane protein 121 (TMEM121), mRNA [NM_025268]	chr14		GO:0016020(membrane);GO:0016021(integral to membrane)	
A_23_P215096	NM_003344	UBE2H	NM_003344	Homo sapiens ubiquitin-conjugating enzyme E2H (UBC8 homolog, yeast) (UBE2H), transcript variant 1, mRNA [NM_003344]	chr7	GO:0006464(protein modification process);GO:0006511(ubiquitin-dependent protein catabolic process);GO:0006512(ubiquitin cycle)		GO:0004842(ubiquitin-protein ligase activity);GO:0016874(ligase activity);GO:0019787(small conjugating protein ligase activity)
A_24_P225534	NM_017821	RHBDL2	NM_017821	Homo sapiens rhomboid, veinlet-like 2 (Drosophila) (RHBDL2), mRNA [NM_017821]	chr1		GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0004252(serine-type endopeptidase activity);GO:0008233(peptidase activity)
A_32_P4608	A_32_P4608	A_32_P4608			chr5			
A_23_P56898	NM_003937	KYNU	NM_003937	Homo sapiens kynureninase (L-kynurenine hydrolase) (KYNU), transcript variant 1, mRNA [NM_003937]	chr2	GO:0006569(tryptophan catabolic process);GO:0008152(metabolic process);GO:0009435(NAD biosynthetic process)	GO:0005737(cytoplasm)	GO:0008233(peptidase activity);GO:0008483(transaminase activity);GO:0016787(hydrolase activity);GO:0030170(pyridoxal phosphate binding);GO:0030429(kynureninase activity)
A_32_P75094	NM_032797	AIFM2	NM_032797	Homo sapiens apoptosis-inducing factor, mitochondrion-associated, 2 (AIFM2), mRNA [NM_032797]	chr10	GO:0006118(electron transport);GO:0006915(apoptosis);GO:0006917(induction of apoptosis);GO:0008152(metabolic process);GO:0008637(apoptotic mitochondrial changes);GO:0030261(chromosome condensation)	GO:0005737(cytoplasm);GO:0005739(mitochondrion);GO:0005741(mitochondrial outer membrane);GO:0005829(cytosol);GO:0016020(membrane);GO:0016021(integral to membrane);GO:0019867(outer membrane)	GO:0003677(DNA binding);GO:0004174(electron-transferring-flavoprotein dehydrogenase activity);GO:0016491(oxidoreductase activity);GO:0050660(FAD binding)
A_23_P374315	NM_153218	C13orf31	NM_153218	Homo sapiens chromosome 13 open reading frame 31 (C13orf31), mRNA [NM_153218]	chr13			
A_23_P77223	NM_018670	MESP1	NM_018670	Homo sapiens mesoderm posterior 1 homolog (mouse) (MESP1), mRNA [NM_018670]	chr15	GO:0045449(regulation of transcription)	GO:0005634(nucleus)	GO:0030528(transcription regulator activity)
A_23_P61945	NM_198159	MITF	NM_198159	Homo sapiens microphthalmia-associated transcription factor (MITF), transcript variant 1, mRNA [NM_198159]	chr3	GO:0006355(regulation of transcription, DNA-dependent);GO:0007275(multicellular organismal development);GO:0007605(sensory perception of sound);GO:0030318(melanocyte differentiation)	GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0016563(transcriptional activator activity)
A_23_P122174	NM_022550	XRCC4	NM_022550	Homo sapiens X-ray repair complementing defective repair in Chinese hamster cells 4 (XRCC4), transcript variant 3, mRNA [NM_022550]	chr5	GO:0006303(double-strand break repair via nonhomologous end joining);GO:0006310(DNA recombination)	GO:0005634(nucleus)	GO:0005515(protein binding)
A_23_P487	NM_012474	UCK2	NM_012474	Homo sapiens uridine-cytidine kinase 2 (UCK2), mRNA [NM_012474]	chr1	GO:0008150(biological_process);GO:0009058(biosynthetic process)	GO:0005575(cellular_component)	GO:0000166(nucleotide binding);GO:0003674(molecular_function);GO:0004849(uridine kinase activity);GO:0005524(ATP binding);GO:0016301(kinase activity);GO:0016740(transferase activity)
A_23_P21473	NM_024491	CEP70	NM_024491	Homo sapiens centrosomal protein 70kDa (CEP70), mRNA [NM_024491]	chr3			
A_24_P134488	NM_052880	PIK3IP1	NM_052880	Homo sapiens HGFL gene (MGC17330), mRNA [NM_052880]	chr22		GO:0016020(membrane);GO:0016021(integral to membrane)	
A_23_P68966	AK090725	AK090725	AK090725	Homo sapiens cDNA FLJ33406 fis, clone BRACE2010477. [AK090725]	chr22			
A_23_P143906	NM_022443	MLF1	NM_022443	Homo sapiens myeloid leukemia factor 1 (MLF1), mRNA [NM_022443]	chr3	GO:0006350(transcription);GO:0007050(cell cycle arrest);GO:0007275(multicellular organismal development);GO:0030154(cell differentiation)	GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0003677(DNA binding);GO:0005515(protein binding);GO:0019904(protein domain specific binding)
A_23_P52402	NM_014889	PITRM1	NM_014889	Homo sapiens pitrilysin metallopeptidase 1 (PITRM1), mRNA [NM_014889]	chr10	GO:0006508(proteolysis)	GO:0005739(mitochondrion);GO:0005759(mitochondrial matrix)	GO:0004222(metalloendopeptidase activity);GO:0008047(enzyme activator activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P408195	NM_152399	TMEM155	NM_152399	Homo sapiens transmembrane protein 155 (TMEM155), mRNA [NM_152399]	chr4			
A_23_P39684	NM_012290	TLK1	NM_012290	Homo sapiens tousled-like kinase 1 (TLK1), mRNA [NM_012290]	chr2	GO:0001672(regulation of chromatin assembly or disassembly);GO:0006468(protein amino acid phosphorylation);GO:0006886(intracellular protein transport);GO:0006974(response to DNA damage stimulus);GO:0007049(cell cycle);GO:0007242(intracellular signaling cascade);GO:0016568(chromatin modification)	GO:0005575(cellular_component);GO:0005634(nucleus)	GO:0000166(nucleotide binding);GO:0004674(protein serine/threonine kinase activity);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0016740(transferase activity)
A_23_P32938	NM_004398	DDX10	NM_004398	Homo sapiens DEAD (Asp-Glu-Ala-Asp) box polypeptide 10 (DDX10), mRNA [NM_004398]	chr11			GO:0000166(nucleotide binding);GO:0003723(RNA binding);GO:0003724(RNA helicase activity);GO:0005524(ATP binding);GO:0008026(ATP-dependent helicase activity);GO:0016787(hydrolase activity)
A_24_P74828	AF348994	MT1JP	AF348994	Homo sapiens MTB (MTB) mRNA, complete cds. [AF348994]	chr16			GO:0046872(metal ion binding)

A_32_P46571	NM_017821	RHBDL2	NM_017821	Homo sapiens rhomboid, veinlet-like 2 (Drosophila) (RHBDL2), mRNA [NM_017821]	chr1		GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0004252(serine-type endopeptidase activity);GO:0008233(peptidase activity)
A_23_P45324	NM_021637	TMEM35	NM_021637	Homo sapiens transmembrane protein 35 (TMEM35), mRNA [NM_021637]	chrX		GO:0016020(membrane);GO:0016021(integral to membrane)	
A_23_P210482	NM_000022	ADA	NM_000022	Homo sapiens adenosine deaminase (ADA), mRNA [NM_000022]	chr20	GO:0006163(purine nucleotide metabolic process);GO:0006955(immune response);GO:0009168(purine ribonucleoside monophosphate biosynthetic process)	GO:0005737(cytoplasm)	GO:0004000(adenosine deaminase activity);GO:0016787(hydrolase activity)
A_23_P93938	ENST00000258775	NACAD		Homo sapiens mRNA for KIAA0363 gene, partial cds. [AB002361]	chr7	GO:0015031(protein transport)	GO:0005634(nucleus)	
A_24_P193509	NM_144600	C16orf63	NM_144600	Homo sapiens chromosome 16 open reading frame 63 (C16orf63), mRNA [NM_144600]	chr16			
A_23_P138541	NM_003739	AKR1C3	NM_003739	Homo sapiens aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II) (AKR1C3), mRNA [NM_003739]	chr10	GO:0006118(electron transport);GO:0006693(prostaglandin metabolic process)	GO:0005622(intracellular)	GO:0004033(aldo-keto reductase activity);GO:0004303(estradiol 17-beta-dehydrogenase activity);GO:0016491(oxidoreductase activity);GO:0047017(prostaglandin-F synthase activity);GO:0047026(3-alpha-hydroxysteroid dehydrogenase (A-specific) activity);GO:0047115(trans-1,2-dihydrobenzene-1,2-diol dehydrogenase activity)
A_23_P94434	NM_001039792	UNQ338	NM_001039792	Homo sapiens LGLL338 (LOC646962), mRNA [NM_001039792]	chr9			
A_23_P147495	NM_021946	BCORL1	NM_021946	Homo sapiens BCL6 co-repressor-like 1 (BCORL1), mRNA [NM_021946]	chrX			
A_24_P345679	AY848702	MLF1	AY848702	Homo sapiens myeloid leukemia factor 1 variant 3 (MLF1) mRNA, complete cds, alternatively spliced. [AY848702]	chr3	GO:0006350(transcription);GO:0007050(cell cycle arrest);GO:0007275(multicellular organismal development);GO:0030154(cell differentiation)	GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0003677(DNA binding);GO:0005515(protein binding);GO:0019904(protein domain specific binding)
A_32_P88415	NM_133371	MYOZ3	NM_133371	Homo sapiens myozenin 3 (MYOZ3), mRNA [NM_133371]	chr5			GO:0005198(structural molecule activity);GO:0005515(protein binding)
A_23_P341223	NM_014851	KLHL21	NM_014851	Homo sapiens kelch-like 21 (Drosophila) (KLHL21), mRNA [NM_014851]	chr1			GO:0005515(protein binding)
A_24_P312578	BC040210	AKR1C1	BC040210	Homo sapiens aldo-keto reductase family 1, member C1 (dihydrodiol dehydrogenase 1; 20-alpha (3-alpha)-hydroxysteroid dehydrogenase), mRNA (cDNA clone MGC:42600 IMAGE:4825338), complete cds. [BC040210]	chr10	GO:0006118(electron transport);GO:0006805(xenobiotic metabolic process);GO:0007586(digestion);GO:0008206(bile acid metabolic process);GO:0015721(bile acid and bile salt transport);GO:0030299(cholesterol absorption);GO:0042632(cholesterol homeostasis);GO:0051260(protein homooligomerization)	GO:0005829(cytosol)	GO:0004033(aldo-keto reductase activity);GO:0016491(oxidoreductase activity);GO:0047006(20-alpha-hydroxysteroid dehydrogenase activity);GO:0047042(3-alpha-hydroxysteroid dehydrogenase (B-specific) activity);GO:0047115(trans-1,2-dihydrobenzene-1,2-diol dehydrogenase activity)
A_23_P35617	NM_016341	PLCE1	NM_016341	Homo sapiens phospholipase C, epsilon 1 (PLCE1), mRNA [NM_016341]	chr10	GO:0000187(activation of MAPK activity);GO:0001558(regulation of cell growth);GO:0006629(lipid metabolic process);GO:0006644(phospholipid metabolic process);GO:0006651(diacylglycerol biosynthetic process);GO:0006940(regulation of smooth muscle contraction);GO:0007010(cytoskeleton organization and biogenesis);GO:0007173(epidermal growth factor receptor signaling pathway);GO:0007204(elevation of cytosolic calcium ion concentration);GO:0007205(protein kinase C activation);GO:0007264(small GTPase mediated signal transduction);GO:0007507(heart development);GO:0008277(regulation of G-protein coupled receptor protein signaling pathway);GO:0008283(cell proliferation);GO:0016042(lipid catabolic process);GO:0019722(calcium-mediated signaling);GO:0045859(regulation of protein kinase activity);GO:0046578(regulation of Ras protein signal transduction);GO:0048016(inositol phosphate-mediated signaling)	GO:0005622(intracellular);GO:0005624(membrane fraction);GO:0005829(cytosol);GO:0005886(plasma membrane)	GO:0004435(phosphoinositide phospholipase C activity);GO:0005057(receptor signaling protein activity);GO:0005085(guanyl-nucleotide exchange factor activity);GO:0005509(calcium ion binding);GO:0016787(hydrolase activity);GO:0017016(Ras GTPase binding);GO:0019899(enzyme binding)
A_32_P149416	BG001037	BG001037	BG001037	BG001037 RC5-GN0132-131100-012-E05 GN0132 Homo sapiens cDNA, mRNA sequence [BG001037]	chr12			
A_24_P767725	XR_017120	LOC646090	XR_017120	PREDICTED: Homo sapiens similar to rhophilin-like protein (LOC646090), mRNA [XR_017120]	chr15			
A_24_P187218	NM_020403	PCDH9	NM_020403	Homo sapiens protocadherin 9 (PCDH9), transcript variant 2, mRNA [NM_020403]	chr13	GO:0007155(cell adhesion);GO:0007156(homophilic cell adhesion)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005509(calcium ion binding);GO:0005515(protein binding)
A_23_P115052	NM_006912	RIT1	NM_006912	Homo sapiens Ras-like without CAAX 1 (RIT1), mRNA [NM_006912]	chr1	GO:0007165(signal transduction);GO:0007264(small GTPase mediated signal transduction)	GO:0005622(intracellular);GO:0005886(plasma membrane);GO:0016020(membrane)	GO:0000166(nucleotide binding);GO:0005516(calmodulin binding);GO:0005525(GTP binding)
A_23_P36689	NM_006992	LRRC23	NM_006992	Homo sapiens leucine rich repeat containing 23 (LRRC23), transcript variant 2, mRNA [NM_006992]	chr12	GO:0008150(biological_process)	GO:0005575(cellular_component)	GO:0003674(molecular_function);GO:0005515(protein binding)

A_23_P390044	NM_002359	MAFG	NM_002359	Homo sapiens v-maf musculoaponeurotic fibrosarcoma oncogene homolog G (avian) (MAFG), transcript variant 1, mRNA [NM_002359]	chr17	GO:0001701(in utero embryonic development);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006366(transcription from RNA polymerase II promoter);GO:0030534(adult behavior);GO:0042127(regulation of cell proliferation);GO:0045604(regulation of epidermal cell differentiation)	GO:0000785(chromatin);GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0046983(protein dimerization activity)
A_23_P332326	NM_153213	ARHGEF19	NM_153213	Homo sapiens Rho guanine nucleotide exchange factor (GEF) 19 (ARHGEF19), mRNA [NM_153213]	chr1	GO:0035023(regulation of Rho protein signal transduction)	GO:0005622(intracellular)	GO:0005085(guanyl-nucleotide exchange factor activity);GO:0005089(Rho guanyl-nucleotide exchange factor activity)
A_23_P106922	NM_021615	CHST6	NM_021615	Homo sapiens carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 6 (CHST6), mRNA [NM_021615]	chr16	GO:0005975(carbohydrate metabolic process);GO:0006044(N-acetylglucosamine metabolic process);GO:0006790(sulfur metabolic process);GO:0018146(keratan sulfate biosynthetic process)	GO:0005794(Golgi apparatus);GO:0016020(membrane);GO:0016021(integral to membrane);GO:0031228(intrinsic to Golgi membrane)	GO:0001517(N-acetylglucosamine 6-O-sulfotransferase activity);GO:0016740(transferase activity)
A_23_P358597	NM_022361	POPDC3	NM_022361	Homo sapiens popeye domain containing 3 (POPDC3), mRNA [NM_022361]	chr6	GO:0008150(biological_process)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0003674(molecular_function)
A_24_P920388	THC2611140	THC2611140		O96938_CERCA (O96938) Acidic ribosomal protein, partial (16%) [THC2611140]	chr12			
A_23_P202100	A_23_P202100	A_23_P202100						
A_23_P52410	NM_145307	PLEKHK1	NM_145307	Homo sapiens pleckstrin homology domain containing, family K member 1 (PLEKHK1), mRNA [NM_145307]	chr10	GO:0007165(signal transduction)	GO:0005622(intracellular)	

D.2 Shear Stress-Responsive Microarrays

D.2.1 Conserved Shear Stress-Responsive Genes

Table 15: Conserved shear-responsive genes identified using two factor ANOVA and paired t-tests of ECs and MSCs. 'Conserved' shear-responsive genes were defined as those meeting three criteria: (1) significant force-dependent gene expression (two factor ANOVA corrected p-value< 0.05), (2) significant (paired t-test p< 0.05) regulation change of at least 1.5-fold in ECs, and (3) significant (paired t-test p< 0.05) regulation change of at least 1.5-fold in MSCs. 574 probes met all three criteria, including 37 with no GenBank Accession information and 91 instances of duplicate genes due to different microarray probes. The following information is listed, as available, for each probe: identifying information (Agilent Probe Name, common name, gene symbol, GenBank Accession number, gene description), genomic position (chromosome number), and Gene Ontology associations (biological processes, cellular components, molecular functions).

Probe Name	Common name	Gene Symbol	Genbank Accession	Description	Chromosome No. (Avadis)	GO biological process	GO cellular component	GO molecular function
Highly Significantly Shear-Responsive Genes, p<0.01 (ANOVA corrected pForce<0.05; EC paired t-test p<0.01; MSC paired t-test p<0.01) - 100 genes								
A_23_P170719	A_23_P170719	A_23_P170719			chr19			
A_32_P4882	A_32_P4882	A_32_P4882			chr4			
A_32_P75141	A_32_P75141	A_32_P75141			chr1			
A_23_P200015	NM_174858	AK5	NM_174858	Homo sapiens adenylate kinase 5 (AK5), transcript variant 1, mRNA [NM_174858]	chr1	GO:0006139(nucleobase, nucleoside, nucleotide and nucleic acid metabolic process);GO:0006172(ADP biosynthetic process);GO:0006173(dADP biosynthetic process);GO:0009220(pyrimidine ribonucleotide biosynthetic process);GO:0046034(ATP metabolic process)	GO:0005737(cytoplasm);GO:0005829(cytosol)	GO:0000166(nucleotide binding);GO:0004017(adenylate kinase activity);GO:0005524(ATP binding);GO:0016301(kinase activity);GO:0016740(transferase activity);GO:0019206(nucleoside kinase activity)
A_23_P112481	NM_004925	AQP3	NM_004925	Homo sapiens aquaporin 3 (Gill blood group) (AQP3), mRNA [NM_004925]	chr9	GO:0006810(transport);GO:0007588(excretion)	GO:0005624(membrane fraction);GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0005215(transporter activity)
A_23_P112482	NM_004925	AQP3	NM_004925	Homo sapiens aquaporin 3 (Gill blood group) (AQP3), mRNA [NM_004925]	chr9	GO:0006810(transport);GO:0007588(excretion)	GO:0005624(membrane fraction);GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0005215(transporter activity)
A_23_P152753	AY358101	AY358101	AY358101	Homo sapiens clone DNA108695 Wpep3002 (UNQ3002) mRNA, complete cds. [AY358101]	chr17			
A_23_P101380	NM_198540	B3GNT8	NM_198540	Homo sapiens UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 8 (B3GNT8), mRNA [NM_198540]	chr19	GO:0006486(protein amino acid glycosylation);GO:0030311(poly-N-acetyllactosamine biosynthetic process)	GO:0016020(membrane)	GO:0008378(galactosyltransferase activity);GO:0016262(protein N-acetylglucosaminyltransferase activity);GO:0016757(transferase activity, transferring glycosyl groups)
A_24_P170874	BC013295	BC013295	BC013295	Homo sapiens cDNA clone IMAGE:2960340. [BC013295]	chr2			
A_32_P72181	BC035184	BC035184	BC035184	Homo sapiens cDNA clone IMAGE:5266408. [BC035184]	chr18			
A_32_P7316	NM_170735	BDNF	NM_170735	Homo sapiens brain-derived neurotrophic factor (BDNF), transcript variant 1, mRNA [NM_170735]	chr11	GO:0001657(ureteric bud development);GO:0006916(anti-apoptosis);GO:0007406(negative regulation of neuroblast proliferation);GO:0007411(axon guidance);GO:0007412(axon target recognition);GO:0007631(feeding behavior);GO:0008038(neuron recognition);GO:0016358(dendrite development);GO:0019222(regulation of metabolic process);GO:0042490(mechanoreceptor differentiation);GO:0045666(positive regulation of neuron differentiation);GO:0046668(regulation of retinal programmed cell death);GO:0048167(regulation of synaptic plasticity)	GO:0016023(cytoplasmic membrane-bound vesicle)	GO:0005515(protein binding);GO:0008083(growth factor activity)
A_23_P99452	NM_000059	BRCA2	NM_000059	Homo sapiens breast cancer 2, early onset (BRCA2), mRNA [NM_000059]	chr13	GO:0000074(regulation of progression through cell cycle);GO:0000724(double-strand break repair via homologous recombination);GO:0006281(DNA repair);GO:0006325(establishment and/or maintenance of chromatin architecture);GO:0006338(chromatin remodeling);GO:0007090(regulation of S phase of mitotic cell cycle);GO:0007093(mitotic checkpoint);GO:0045449(regulation of transcription)	GO:0005615(extracellular space);GO:0005634(nucleus);GO:0005737(cytoplasm);GO:0030141(secretory granule)	GO:0003697(single-stranded DNA binding);GO:0004402(histone acetyltransferase activity);GO:0005515(protein binding);GO:0016563(transcriptional activator activity)
A_23_P26557	NM_025108	C16orf59	NM_025108	Homo sapiens chromosome 16 open reading frame 59 (C16orf59), mRNA [NM_025108]	chr16			
A_23_P353717	NM_152308	C16orf75	NM_152308	Homo sapiens chromosome 16 open reading frame 75 (C16orf75), mRNA [NM_152308]	chr16			
A_24_P33982	ENST00000332935	C17orf60		Uncharacterized protein C17orf60 (Fragment). [Source:Uniprot/SPTREMBL;Acc:Q7Z6M3] [ENST00000332935]	chr17			
A_23_P300797	NM_173529	C18orf54	NM_173529	Homo sapiens chromosome 18 open reading frame 54 (C18orf54), mRNA [NM_173529]	chr18			
A_24_P6370	BC040018	C1orf110	BC040018	Homo sapiens chromosome 1 open reading frame 110, mRNA (cDNA clone MGC:48998 IMAGE:5753568), complete cds. [BC040018]	chr1			
A_23_P160537	NM_024037	C1orf135	NM_024037	Homo sapiens chromosome 1 open reading frame 135 (C1orf135), mRNA [NM_024037]	chr1			
A_23_P403081	NM_198566	C5orf34	NM_198566	Homo sapiens chromosome 5 open reading frame 34 (C5orf34), mRNA [NM_198566]	chr5			
A_23_P405754	NM_000723	CACNB1	NM_000723	Homo sapiens calcium channel, voltage-dependent, beta 1 subunit (CACNB1), transcript variant 1, mRNA [NM_000723]	chr17	GO:0006811(ion transport);GO:0006816(calcium ion transport);GO:0006936(muscle contraction)	GO:0005624(membrane fraction);GO:0005891(voltage-gated calcium channel complex)	GO:0005245(voltage-gated calcium channel activity);GO:0005509(calcium ion binding)

A_23_P134454	NM_001753	CAV1	NM_001753	Homo sapiens caveolin 1, caveolae protein, 22kDa (CAV1), mRNA [NM_001753]	chr7	GO:0000188(inactivation of MAPK activity);GO:0001937(negative regulation of endothelial cell proliferation);GO:0006641(triacylglycerol metabolic process);GO:0009968(negative regulation of signal transduction);GO:0019217(regulation of fatty acid metabolic process);GO:0019915(sequestering of lipid);GO:0030301(cholesterol transport);GO:0042632(cholesterol homeostasis);GO:0045019(negative regulation of nitric oxide biosynthetic process);GO:0045907(positive regulation of vasoconstriction);GO:0045908(negative regulation of vasodilation);GO:0051260(protein homooligomerization)	GO:0000139(Golgi membrane);GO:0000299(integral to membrane of membrane fraction);GO:0005783(endoplasmic reticulum);GO:0005886(plasma membrane);GO:0005887(integral to plasma membrane);GO:0016021(integral to membrane);GO:0016599(caveolar membrane);GO:0045121(lipid raft);GO:0048471(perinuclear region of cytoplasm)	GO:0005198(structural molecule activity);GO:0005515(protein binding);GO:0015485(cholesterol binding)
A_23_P311144	NM_144978	CCDC138	NM_144978	Homo sapiens hypothetical protein FLJ32745 (FLJ32745), mRNA [NM_144978]	chr2			
A_24_P397107	NM_001789	CDC25A	NM_001789	Homo sapiens cell division cycle 25 homolog A (S. pombe) (CDC25A), transcript variant 1, mRNA [NM_001789]	chr3	GO:0000079(regulation of cyclin-dependent protein kinase activity);GO:0006470(protein amino acid dephosphorylation);GO:0007049(cell cycle);GO:0007067(mitosis);GO:0008283(cell proliferation);GO:0051301(cell division)	GO:0005575(cellular_component);GO:0005622(intracellular)	GO:0004725(protein tyrosine phosphatase activity);GO:0005515(protein binding);GO:0016787(hydrolase activity)
A_23_P352426	NM_006382	CDRT1	NM_006382	Homo sapiens CMT1A duplicated region transcript 1 (CDRT1), mRNA [NM_006382]	chr17	GO:0008150(biological_process)	GO:0005575(cellular_component)	GO:0003674(molecular_function)
A_23_P21473	NM_024491	CEP70	NM_024491	Homo sapiens centrosomal protein 70kDa (CEP70), mRNA [NM_024491]	chr3			
A_24_P53519	NM_005483	CHAF1A	NM_005483	Homo sapiens chromatin assembly factor 1, subunit A (p150) (CHAF1A), mRNA [NM_005483]	chr19	GO:0006260(DNA replication);GO:0006281(DNA repair);GO:0006335(DNA replication-dependent nucleosome assembly);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006457(protein folding);GO:0006461(protein complex assembly);GO:0007049(cell cycle)	GO:0005634(nucleus);GO:0005678(chromatin assembly complex)	GO:0003682(chromatin binding);GO:0051082(unfolded protein binding)
A_23_P57306	NM_005441	CHAF1B	NM_005441	Homo sapiens chromatin assembly factor 1, subunit B (p60) (CHAF1B), mRNA [NM_005441]	chr21	GO:0006260(DNA replication);GO:0006281(DNA repair);GO:0006335(DNA replication-dependent nucleosome assembly);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006461(protein complex assembly);GO:0007049(cell cycle)	GO:0005634(nucleus);GO:0005678(chromatin assembly complex);GO:0005737(cytoplasm)	GO:0003682(chromatin binding);GO:0042393(histone binding);GO:0051082(unfolded protein binding)
A_32_P44274	NM_022092	CHTF18	NM_022092	Homo sapiens CTF18, chromosome transmission fidelity factor 18 homolog (S. cerevisiae) (CHTF18), mRNA [NM_022092]	chr16			GO:0000166(nucleotide binding);GO:0004386(helicase activity);GO:0005524(ATP binding);GO:0017111(nucleoside-triphosphatase activity)
A_23_P354297	NM_022092	CHTF18	NM_022092	Homo sapiens CTF18, chromosome transmission fidelity factor 18 homolog (S. cerevisiae) (CHTF18), mRNA [NM_022092]	chr16			GO:0000166(nucleotide binding);GO:0004386(helicase activity);GO:0005524(ATP binding);GO:0017111(nucleoside-triphosphatase activity)
A_24_P99090	NM_018204	CKAP2	NM_018204	Homo sapiens cytoskeleton associated protein 2 (CKAP2), mRNA [NM_018204]	chr13	GO:0006915(apoptosis);GO:0007049(cell cycle)	GO:0005874(microtubule)	
A_23_P210100	NM_019885	CYP26B1	NM_019885	Homo sapiens cytochrome P450, family 26, subfamily B, polypeptide 1 (CYP26B1), mRNA [NM_019885]	chr2	GO:0006118(electron transport);GO:0009954(proximal/distal pattern formation);GO:0030326(embryonic limb morphogenesis);GO:0048384(retinoic acid receptor signaling pathway)	GO:0005783(endoplasmic reticulum);GO:0005792(microsome);GO:0016020(membrane)	GO:0004497(monooxygenase activity);GO:0005506(iron ion binding);GO:0020037(heme binding);GO:0046872(metal ion binding)
A_23_P254612	NM_006716	DBF4	NM_006716	Homo sapiens DBF4 homolog (S. cerevisiae) (DBF4), mRNA [NM_006716]	chr7	GO:0000074(regulation of progression through cell cycle);GO:0000082(G1/S transition of mitotic cell cycle);GO:0006260(DNA replication);GO:0007049(cell cycle)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003676(nucleic acid binding);GO:0005515(protein binding);GO:0008047(enzyme activator activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P252740	NM_024094	DCC1	NM_024094	Homo sapiens defective in sister chromatid cohesion homolog 1 (S. cerevisiae) (DCC1), mRNA [NM_024094]	chr8			
A_23_P369994	NM_004734	DCLK1	NM_004734	Homo sapiens doublecortin and CaM kinase-like 1 (DCAMKL1), mRNA [NM_004734]	chr13	GO:0006468(protein amino acid phosphorylation);GO:0007242(intracellular signaling cascade);GO:0007275(multicellular organismal development);GO:0007417(central nervous system development);GO:0016197(endosome transport);GO:0030154(cell differentiation)	GO:0005887(integral to plasma membrane)	GO:0000166(nucleotide binding);GO:0004674(protein serine/threonine kinase activity);GO:0005057(receptor signaling protein activity);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0016301(kinase activity);GO:0016740(transferase activity)
A_23_P254702	NM_003472	DEK	NM_003472	Homo sapiens DEK oncogene (DNA binding) (DEK), mRNA [NM_003472]	chr6	GO:0006357(regulation of transcription from RNA polymerase II promoter);GO:0007165(signal transduction);GO:0019079(viral genome replication)	GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0003704(specific RNA polymerase II transcription factor activity);GO:0042393(histone binding)
A_24_P343095	NM_000791	DHFR	NM_000791	Homo sapiens dihydrofolate reductase (DHFR), mRNA [NM_000791]	chr5	GO:0006545(glycine biosynthetic process);GO:0006730(one-carbon compound metabolic process);GO:0009165(nucleotide biosynthetic process)	GO:0005575(cellular_component)	GO:0004146(dihydrofolate reductase activity);GO:0016491(oxidoreductase activity);GO:0050661(NADP binding)
A_23_P33759	NM_004753	DHRS3	NM_004753	Homo sapiens dehydrogenase/reductase (SDR family) member 3 (DHRS3), mRNA [NM_004753]	chr1	GO:0007601(visual perception);GO:0008152(metabolic process);GO:0042572(retinol metabolic process)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0000166(nucleotide binding);GO:0009055(electron carrier activity);GO:0016491(oxidoreductase activity)

A_23_P425502	NM_017613	DONSON	NM_017613	Homo sapiens downstream neighbor of SON (DONSON), mRNA [NM_017613]	chr21	GO:0007275(multicellular organismal development);GO:0008150(biological_process)	GO:0005575(cellular_component);GO:0005634(nucleus)	GO:0003674(molecular_function)
A_23_P139704	NM_001946	DUSP6	NM_001946	Homo sapiens dual specificity phosphatase 6 (DUSP6), transcript variant 1, mRNA [NM_001946]	chr12	GO:0000074(regulation of progression through cell cycle);GO:0000188(inactivation of MAPK activity);GO:0006470(protein amino acid dephosphorylation)	GO:0005625(soluble fraction);GO:0005737(cytoplasm)	GO:0004722(protein serine/threonine phosphatase activity);GO:0004725(protein tyrosine phosphatase activity);GO:0016787(hydrolase activity);GO:0017017(MAP kinase phosphatase activity)
A_23_P93737	NM_004411	DYNC1I1	NM_004411	Homo sapiens dynein, cytoplasmic 1, intermediate chain 1 (DYNC1I1), mRNA [NM_004411]	chr7	GO:0047496(vesicle transport along microtubule)	GO:0005868(cytoplasmic dynein complex);GO:0005874(microtubule);GO:0048471(perinuclear region of cytoplasm)	GO:0003777(microtubule motor activity);GO:0005515(protein binding);GO:0008017(microtubule binding)
A_23_P44684	NM_018098	ECT2	NM_018098	Homo sapiens epithelial cell transforming sequence 2 oncogene (ECT2), mRNA [NM_018098]	chr3	GO:0007242(intracellular signaling cascade);GO:0035023(regulation of Rho protein signal transduction);GO:0043123(positive regulation of I-kappaB kinase/NF-kappaB cascade)	GO:0005622(intracellular)	GO:0004871(signal transducer activity);GO:0005085(guanyl-nucleotide exchange factor activity);GO:0005089(Rho guanyl-nucleotide exchange factor activity);GO:0005515(protein binding)
A_23_P214080	NM_001964	EGR1	NM_001964	Homo sapiens early growth response 1 (EGR1), mRNA [NM_001964]	chr5	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0030217(T cell differentiation);GO:0045941(positive regulation of transcription)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P78092	NM_001003927	EVI2A	NM_001003927	Homo sapiens ecotropic viral integration site 2A (EVI2A), transcript variant 1, mRNA [NM_001003927]	chr17		GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0004888(transmembrane receptor activity)
A_23_P66694	NM_006495	EVI2B	NM_006495	Homo sapiens ecotropic viral integration site 2B (EVI2B), mRNA [NM_006495]	chr17		GO:0005887(integral to plasma membrane);GO:0016020(membrane)	
A_23_P212800	NM_004464	FGF5	NM_004464	Homo sapiens fibroblast growth factor 5 (FGF5), transcript variant 1, mRNA [NM_004464]	chr4	GO:0000074(regulation of progression through cell cycle);GO:0007267(cell-cell signaling);GO:0007399(nervous system development);GO:0008283(cell proliferation);GO:0008543(fibroblast growth factor receptor signaling pathway)	GO:0005615(extracellular space)	GO:0008083(growth factor activity)
A_23_P209578	NM_013445	GAD1	NM_013445	Homo sapiens glutamate decarboxylase 1 (brain, 67kDa) (GAD1), transcript variant GAD25, mRNA [NM_013445]	chr2	GO:0006540(glutamate decarboxylation to succinate);GO:0007268(synaptic transmission);GO:0018352(protein-pyridoxal-5-phosphate linkage);GO:0019752(carboxylic acid metabolic process);GO:0042136(neurotransmitter biosynthetic process)	GO:0005622(intracellular);GO:0012506(vesicle membrane)	GO:0004351(glutamate decarboxylase activity);GO:0005515(protein binding);GO:0016829(lyase activity);GO:0016831(carboxy-lyase activity);GO:0030170(pyridoxal phosphate binding)
A_23_P210853	NM_021067	GINS1	NM_021067	Homo sapiens GINS complex subunit 1 (Psf1 homolog) (GINS1), mRNA [NM_021067]	chr20	GO:0006260(DNA replication)	GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0005515(protein binding)
A_23_P118246	NM_016095	GINS2	NM_016095	Homo sapiens GINS complex subunit 2 (Psf2 homolog) (GINS2), mRNA [NM_016095]	chr16	GO:0006260(DNA replication)	GO:0005634(nucleus)	
A_23_P19712	NM_015895	GMNN	NM_015895	Homo sapiens geminin, DNA replication inhibitor (GMNN), mRNA [NM_015895]	chr6	GO:0007049(cell cycle);GO:0008156(negative regulation of DNA replication);GO:0045786(negative regulation of progression through cell cycle)		GO:0005515(protein binding)
A_23_P204375	NM_020400	GPR92	NM_020400	Homo sapiens G protein-coupled receptor 92 (GPR92), mRNA [NM_020400]	chr12	GO:0007165(signal transduction);GO:0007186(G-protein coupled receptor protein signaling pathway);GO:0008150(biological_process)	GO:0005575(cellular_component);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0001584(rhodopsin-like receptor activity);GO:0003674(molecular_function);GO:0004872(receptor activity);GO:0045028(purinergic nucleotide receptor activity, G-protein coupled)
A_23_P12816	NM_018063	HELLS	NM_018063	Homo sapiens helicase, lymphoid-specific (HELLS), mRNA [NM_018063]	chr10	GO:0006346(methylation-dependent chromatin silencing);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0007049(cell cycle);GO:0007067(mitosis);GO:0007275(multicellular organismal development);GO:0010216(maintenance of DNA methylation);GO:0031508(centric heterochromatin formation);GO:0046651(lymphocyte proliferation);GO:0051301(cell division)	GO:0005634(nucleus);GO:0005721(centric heterochromatin)	GO:0000166(nucleotide binding);GO:0003677(DNA binding);GO:0004386(helicase activity);GO:0005524(ATP binding);GO:0016787(hydrolase activity)
A_23_P95930	NM_003483	HMGA2	NM_003483	Homo sapiens high mobility group AT-hook 2 (HMGA2), transcript variant 1, mRNA [NM_003483]	chr12	GO:0006325(establishment and/or maintenance of chromatin architecture);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0007001(chromosome organization and biogenesis (sensu Eukaryota));GO:0007275(multicellular organismal development)	GO:0000785(chromatin);GO:0005634(nucleus);GO:0005694(chromosome)	GO:0003677(DNA binding);GO:0003680(AT DNA binding);GO:0005515(protein binding)
A_23_P56734	NM_006895	HNMT	NM_006895	Homo sapiens histamine N-methyltransferase (HNMT), transcript variant 1, mRNA [NM_006895]	chr2	GO:0007585(respiratory gaseous exchange)		GO:0008168(methyltransferase activity);GO:0016740(transferase activity);GO:0046539(histamine N-methyltransferase activity)
A_23_P254507	NM_139211	HOP	NM_139211	Homo sapiens homeodomain-only protein (HOP), transcript variant 2, mRNA [NM_139211]	chr4	GO:0006355(regulation of transcription, DNA-dependent);GO:0007275(multicellular organismal development)	GO:0005634(nucleus)	GO:0003700(transcription factor activity)
A_23_P150667	NM_031217	KIF18A	NM_031217	Homo sapiens kinesin family member 18A (KIF18A), mRNA [NM_031217]	chr11	GO:0007018(microtubule-based movement);GO:0015031(protein transport)	GO:0005874(microtubule);GO:0005875(microtubule associated complex)	GO:0000166(nucleotide binding);GO:0003777(microtubule motor activity);GO:0005524(ATP binding)
A_23_P44505	NM_003597	KLF11	NM_003597	Homo sapiens Kruppel-like factor 11 (KLF11), mRNA [NM_003597]	chr2	GO:0000122(negative regulation of transcription from RNA polymerase II promoter);GO:0006350(transcription);GO:0006366(transcription from RNA polymerase II promoter);GO:0008285(negative regulation of cell proliferation)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003676(nucleic acid binding);GO:0003700(transcription factor activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P87310	NM_002315	LMO1	NM_002315	Homo sapiens LIM domain only 1 (rhombotin 1) (LMO1), mRNA [NM_002315]	chr11	GO:0007275(multicellular organismal development);GO:0008283(cell proliferation)	GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)

A_24_P68908	BX640843	LOC344887	BX640843	Homo sapiens mRNA; cDNA DKFZp686B14224 (from clone DKFZp686B14224). [BX640843]	chr3			
A_23_P136724	BX640843	LOC344887	BX640843	Homo sapiens mRNA; cDNA DKFZp686B14224 (from clone DKFZp686B14224). [BX640843]	chr3			
A_23_P206501	NM_001011880	LOC497190	NM_001011880	Homo sapiens secretory protein LOC497190 (LOC497190), mRNA [NM_001011880]	chr16		GO:0005576(extracellular region);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005529(sugar binding)
A_23_P201988	NM_032844	MASTL	NM_032844	Homo sapiens microtubule associated serine/threonine kinase-like (MASTL), mRNA [NM_032844]	chr10	GO:0006468(protein amino acid phosphorylation)		GO:0000166(nucleotide binding);GO:0004674(protein serine/threonine kinase activity);GO:0005524(ATP binding);GO:0016740(transferase activity)
A_23_P370989	NM_005914	MCM4	NM_005914	Homo sapiens MCM4 minichromosome maintenance deficient 4 (S. cerevisiae) (MCM4), transcript variant 1, mRNA [NM_005914]	chr8	GO:0006260(DNA replication);GO:0006268(DNA unwinding during replication);GO:0006270(DNA replication initiation);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent)	GO:0005634(nucleus)	GO:0000166(nucleotide binding);GO:0003677(DNA binding);GO:0003678(DNA helicase activity);GO:0003697(single-stranded DNA binding);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0008094(DNA-dependent ATPase activity);GO:0017111(nucleoside-triphosphatase activity)
A_23_P93690	NM_182776	MCM7	NM_182776	Homo sapiens MCM7 minichromosome maintenance deficient 7 (S. cerevisiae) (MCM7), transcript variant 2, mRNA [NM_182776]	chr7	GO:0006260(DNA replication);GO:0006270(DNA replication initiation);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0007049(cell cycle)	GO:0000785(chromatin);GO:0005634(nucleus)	GO:0000166(nucleotide binding);GO:0003677(DNA binding);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0008094(DNA-dependent ATPase activity);GO:0017111(nucleoside-triphosphatase activity)
A_23_P353652	NM_005587	MEF2A	NM_005587	Homo sapiens MADS box transcription enhancer factor 2, polypeptide A (myocyte enhancer factor 2A) (MEF2A), mRNA [NM_005587]	chr15	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006366(transcription from RNA polymerase II promoter);GO:0007517(muscle development)	GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0003713(transcription coactivator activity)
A_23_P94422	NM_014791	MELK	NM_014791	Homo sapiens maternal embryonic leucine zipper kinase (MELK), mRNA [NM_014791]	chr9	GO:0006468(protein amino acid phosphorylation)		GO:0000166(nucleotide binding);GO:0004674(protein serine/threonine kinase activity);GO:0005524(ATP binding);GO:0016740(transferase activity)
A_23_P159986	BC007360	MGC16121	BC007360	Homo sapiens hypothetical protein MGC16121, mRNA (cDNA clone IMAGE:3627113), complete cds. [BC007360]	chrX			
A_23_P19176	NM_206966	MGC23985	NM_206966	Homo sapiens similar to AVLV472 (MGC23985), mRNA [NM_206966]	chr5			
A_23_P31073	NM_005375	MYB	NM_005375	Homo sapiens v-myb myeloblastosis viral oncogene homolog (avian) (MYB), mRNA [NM_005375]	chr6	GO:0006355(regulation of transcription, DNA-dependent);GO:0006397(mRNA processing);GO:0007049(cell cycle);GO:0008380(RNA splicing);GO:0045449(regulation of transcription)	GO:0005634(nucleus);GO:0005681(spliceosome);GO:0016363(nuclear matrix)	GO:0003677(DNA binding);GO:0005515(protein binding);GO:0016563(transcriptional activator activity);GO:0030528(transcription regulator activity)
A_23_P138194	NM_000433	NCF2	NM_000433	Homo sapiens neutrophil cytosolic factor 2 (65kDa, chronic granulomatous disease, autosomal 2) (NCF2), mRNA [NM_000433]	chr1	GO:0006801(superoxide metabolic process);GO:0006968(cellular defense response)	GO:0001669(acrosome);GO:0005625(soluble fraction);GO:0005737(cytoplasm);GO:0005829(cytosol)	GO:0005488(binding);GO:0005515(protein binding);GO:0009055(electron carrier activity)
A_23_P396800	NM_173808	NEGR1	NM_173808	Homo sapiens neuronal growth regulator 1 (NEGR1), mRNA [NM_173808]	chr1	GO:0007155(cell adhesion)	GO:0016020(membrane)	GO:0005515(protein binding);GO:0048503(GPI anchor binding)
A_23_P138686	NM_004808	NMT2	NM_004808	Homo sapiens N-myristoyltransferase 2 (NMT2), mRNA [NM_004808]	chr10	GO:0006499(N-terminal protein myristoylation);GO:0009249(protein-lipoylation)		GO:0004379(glycylpeptide N-tetradecanoyltransferase activity);GO:0008415(acyltransferase activity);GO:0016740(transferase activity)
A_23_P141965	NM_033417	NY-SAR-48	NM_033417	Homo sapiens sarcoma antigen NY-SAR-48 (NY-SAR-48), transcript variant 1, mRNA [NM_033417]	chr19			
A_24_P200427	NM_006452	PAICS	NM_006452	Homo sapiens phosphoribosylaminoimidazole carboxylase, phosphoribosylaminoimidazole succinocarboxamide synthetase (PAICS), transcript variant 2, mRNA [NM_006452]	chr4	GO:0006164(purine nucleotide biosynthetic process);GO:0006189('de novo' IMP biosynthetic process);GO:0009113(purine base biosynthetic process)	GO:0009320(phosphoribosylaminoimidazole carboxylase complex)	GO:0003824(catalytic activity);GO:0004638(phosphoribosylaminoimidazole carboxylase activity);GO:0004639(phosphoribosylaminoimidazolesuccinocarboxamide synthase activity);GO:0005524(ATP binding);GO:0016829(lyase activity);GO:0016874(ligase activity);GO:0042802(identical protein binding)
A_24_P234838	NM_032420	PCDH1	NM_032420	Homo sapiens protocadherin 1 (PCDH1), transcript variant 2, mRNA [NM_032420]	chr5	GO:0006355(regulation of transcription, DNA-dependent);GO:0007155(cell adhesion);GO:0007156(homophilic cell adhesion);GO:0007267(cell-cell signaling);GO:0007399(nervous system development)	GO:0005886(plasma membrane);GO:0005887(integral to plasma membrane);GO:0005911(intercellular junction);GO:0016020(membrane)	GO:0003677(DNA binding);GO:0003711(transcriptional elongation regulator activity);GO:0005509(calcium ion binding);GO:0005515(protein binding)
A_32_P142440	NM_174936	PCSK9	NM_174936	Homo sapiens proprotein convertase subtilisin/kexin type 9 (PCSK9), mRNA [NM_174936]	chr1	GO:0006508(proteolysis);GO:0006629(lipid metabolic process);GO:0008202(steroid metabolic process);GO:0008203(cholesterol metabolic process);GO:0009267(cellular response to starvation);GO:0016540(protein autoprocessing);GO:0030182(neuron differentiation);GO:0042632(cholesterol homeostasis);GO:0043086(negative regulation of enzyme activity)	GO:0005576(extracellular region);GO:0005615(extracellular space)	GO:0004289(subtilase activity);GO:0005509(calcium ion binding);GO:0008233(peptidase activity);GO:0016808(proprotein convertase activity);GO:0042802(identical protein binding);GO:0050750(low-density lipoprotein receptor binding)
A_23_P59338	NM_018945	PDE7B	NM_018945	Homo sapiens phosphodiesterase 7B (PDE7B), mRNA [NM_018945]	chr6	GO:0007165(signal transduction);GO:0007268(synaptic transmission)		GO:0004115(3',5'-cyclic-AMP phosphodiesterase activity);GO:0016787(hydrolase activity)
A_23_P401904	NM_001009936	PHF19	NM_001009936	Homo sapiens PHD finger protein 19 (PHF19), transcript variant 2, mRNA [NM_001009936]	chr9			GO:0003676(nucleic acid binding);GO:0005515(protein binding);GO:0008270(zinc ion binding)

A_23_P50456	NM_002691	POLD1	NM_002691	Homo sapiens polymerase (DNA directed), delta 1, catalytic subunit 125kDa (POLD1), mRNA [NM_002691]	chr19	GO:0000084(S phase of mitotic cell cycle);GO:0000731(DNA synthesis during DNA repair);GO:0006139(nucleobase, nucleoside, nucleotide and nucleic acid metabolic process);GO:0006260(DNA replication);GO:0009411(response to UV)	GO:0005634(nucleus)	GO:0000166(nucleotide binding);GO:0003677(DNA binding);GO:0003682(chromatin binding);GO:0003887(DNA-directed DNA polymerase activity);GO:0003891(delta DNA polymerase activity);GO:0004527(exonuclease activity);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0016740(transferase activity);GO:0016787(hydrolase activity);GO:0046872(metal ion binding)
A_23_P252062	NM_138711	PPARG	NM_138711	Homo sapiens peroxisome proliferator-activated receptor gamma (PPARG), transcript variant 3, mRNA [NM_138711]	chr3	GO:0000122(negative regulation of transcription from RNA polymerase II promoter);GO:0006091(generation of precursor metabolites and energy);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006629(lipid metabolic process);GO:0007165(signal transduction);GO:0007584(response to nutrient);GO:0030855(epithelial cell differentiation);GO:0045165(cell fate commitment);GO:0045598(regulation of fat cell differentiation);GO:0045941(positive regulation of transcription);GO:0045944(positive regulation of transcription from RNA polymerase II promoter);GO:0050872(white fat cell differentiation)	GO:0005634(nucleus);GO:0005829(cytosol)	GO:0003700(transcription factor activity);GO:0003707(steroid hormone receptor activity);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0016563(transcriptional activator activity);GO:0016564(transcriptional repressor activity);GO:0046872(metal ion binding)
A_23_P88362	NM_152329	PPIL5	NM_152329	Homo sapiens peptidylprolyl isomerase (cyclophilin)-like 5 (PPIL5), transcript variant 1, mRNA [NM_152329]	chr14			GO:0005515(protein binding)
A_23_P96641	NM_002765	PRPS2	NM_002765	Homo sapiens phosphoribosyl pyrophosphate synthetase 2 (PRPS2), transcript variant 2, mRNA [NM_002765]	chrX	GO:0009116(nucleoside metabolic process);GO:0009156(ribonucleoside monophosphate biosynthetic process);GO:0009165(nucleotide biosynthetic process)		GO:0000287(magnesium ion binding);GO:0004749(ribose phosphate diphosphokinase activity);GO:0016301(kinase activity);GO:0016740(transferase activity);GO:0016978(lipoate-protein ligase B activity)
A_23_P71558	NM_004260	RECQL4	NM_004260	Homo sapiens RecQ protein-like 4 (RECQL4), mRNA [NM_004260]	chr8	GO:0006281(DNA repair);GO:0006310(DNA recombination);GO:0007275(multicellular organismal development)	GO:0005634(nucleus)	GO:0000166(nucleotide binding);GO:0003676(nucleic acid binding);GO:0003678(DNA helicase activity);GO:0005524(ATP binding);GO:0008026(ATP-dependent helicase activity);GO:0008270(zinc ion binding);GO:0016787(hydrolase activity)
A_23_P93823	NM_181471	RFC2	NM_181471	Homo sapiens replication factor C (activator 1) 2, 40kDa (RFC2), transcript variant 1, mRNA [NM_181471]	chr7	GO:0006260(DNA replication)	GO:0005634(nucleus);GO:0005663(DNA replication factor C complex)	GO:0000166(nucleotide binding);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0017111(nucleoside-triphosphatase activity)
A_23_P95302	NM_181578	RFC5	NM_181578	Homo sapiens replication factor C (activator 1) 5, 36.5kDa (RFC5), transcript variant 2, mRNA [NM_181578]	chr12	GO:0006260(DNA replication);GO:0006281(DNA repair)	GO:0005634(nucleus);GO:0005663(DNA replication factor C complex)	GO:0000166(nucleotide binding);GO:0005524(ATP binding);GO:0017111(nucleoside-triphosphatase activity);GO:0019899(enzyme binding)
A_23_P433855	NM_005613	RGS4	NM_005613	Homo sapiens regulator of G-protein signalling 4 (RGS4), mRNA [NM_005613]	chr1	GO:0000188(inactivation of MAPK activity);GO:0008277(regulation of G-protein coupled receptor protein signaling pathway);GO:0009968(negative regulation of signal transduction)		GO:0004871(signal transducer activity);GO:0005096(GTPase activator activity);GO:0005516(calmodulin binding)
A_24_P40306	NM_000185	SERPIND1	NM_000185	Homo sapiens serpin peptidase inhibitor, clade D (heparin cofactor), member 1 (SERPIND1), mRNA [NM_000185]	chr22	GO:0006935(chemotaxis);GO:0007596(blood coagulation)	GO:0005576(extracellular region)	GO:0004867(serine-type endopeptidase inhibitor activity);GO:0008201(heparin binding)
A_23_P29083	NM_194255	SLC19A1	NM_194255	Homo sapiens solute carrier family 19 (folate transporter), member 1 (SLC19A1), mRNA [NM_194255]	chr21	GO:0006810(transport);GO:0015884(folic acid transport)	GO:0005624(membrane fraction);GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0005542(folic acid binding);GO:0008517(folic acid transporter activity);GO:0008518(reduced folate carrier activity);GO:0015350(methotrexate transporter activity)
A_23_P91900	NM_005496	SMC4	NM_005496	Homo sapiens structural maintenance of chromosomes 4 (SMC4), transcript variant 1, mRNA [NM_005496]	chr3	GO:0006259(DNA metabolic process);GO:0007001(chromosome organization and biogenesis (sensu Eukaryota));GO:0007049(cell cycle);GO:0007076(mitotic chromosome condensation);GO:0051301(cell division)	GO:0000796(condensin complex);GO:0005634(nucleus);GO:0005694(chromosome)	GO:0000166(nucleotide binding);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0046982(protein heterodimerization activity)
A_32_P127153	NM_003104	SORD	NM_003104	Homo sapiens sorbitol dehydrogenase (SORD), mRNA [NM_003104]	chr15	GO:0006060(sorbitol metabolic process);GO:0007601(visual perception)		GO:0003939(L-iditol 2-dehydrogenase activity);GO:0008270(zinc ion binding);GO:0016491(oxidoreductase activity);GO:0046872(metal ion binding)
A_32_P28872	NM_006755	TALDO1	NM_006755	Homo sapiens transaldolase 1 (TALDO1), mRNA [NM_006755]	chr11	GO:0005975(carbohydrate metabolic process);GO:0006098(pentose-phosphate shunt);GO:0008152(metabolic process)	GO:0005737(cytoplasm)	GO:0003824(catalytic activity);GO:0004801(transaldolase activity);GO:0005515(protein binding);GO:0016740(transferase activity)
A_24_P542489	THC2531064	THC2531064		ALU7_HUMAN (P39194) Alu subfamily SQ sequence contamination warning entry, partial (11%) [THC2531064]	chr11			
A_23_P9293	NM_004817	TJP2	NM_004817	Homo sapiens tight junction protein 2 (zona occludens 2) (TJP2), transcript variant 1, mRNA [NM_004817]	chr9		GO:0005634(nucleus);GO:0005887(integral to plasma membrane);GO:0005923(tight junction);GO:0016020(membrane)	GO:0004385(guanylate kinase activity);GO:0005515(protein binding)
A_23_P61633	NM_005781	TNK2	NM_005781	Homo sapiens tyrosine kinase, non-receptor, 2 (TNK2), transcript variant 1, mRNA [NM_005781]	chr3	GO:0006468(protein amino acid phosphorylation);GO:0007010(cytoskeleton organization and biogenesis);GO:0007264(small GTPase mediated signal transduction);GO:0050731(positive regulation of peptidyl-tyrosine phosphorylation)	GO:0005737(cytoplasm)	GO:0000166(nucleotide binding);GO:0004713(protein-tyrosine kinase activity);GO:0004715(non-membrane spanning protein tyrosine kinase activity);GO:0005095(GTPase inhibitor activity);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0016740(transferase activity)

A_23_P160598	BC009364	TOE1	BC009364	Homo sapiens target of EGR1, member 1 (nuclear), mRNA (cDNA clone MGC:14971 IMAGE:4302712), complete cds. [BC009364]	chr1		GO:0005634(nucleus)	GO:0003676(nucleic acid binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P5392	NM_004881	TP53I3	NM_004881	Homo sapiens tumor protein p53 inducible protein 3 (TP53I3), transcript variant 1, mRNA [NM_004881]	chr2	GO:0008631(induction of apoptosis by oxidative stress)	GO:0005575(cellular_component)	GO:0003674(molecular_function);GO:0008270(zinc ion binding);GO:0016491(oxidoreductase activity)
A_23_P208880	NM_013282	UHRF1	NM_013282	Homo sapiens ubiquitin-like, containing PHD and RING finger domains, 1 (UHRF1), transcript variant 2, mRNA [NM_013282]	chr19	GO:0006281(DNA repair);GO:0006350(transcription);GO:0006357(regulation of transcription from RNA polymerase II promoter);GO:0006464(protein modification process);GO:0006512(ubiquitin cycle);GO:0007049(cell cycle);GO:0008283(cell proliferation)	GO:0005634(nucleus)	GO:0003676(nucleic acid binding);GO:0003700(transcription factor activity);GO:0003702(RNA polymerase II transcription factor activity);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0008907(integrase activity);GO:0016874(ligase activity);GO:0046872(metal ion binding)
A_23_P389919	NM_133330	WHSC1	NM_133330	Homo sapiens Wolf-Hirschhorn syndrome candidate 1 (WHSC1), transcript variant 1, mRNA [NM_133330]	chr4	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0009653(anatomical structure morphogenesis);GO:0016568(chromatin modification)	GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0005515(protein binding);GO:0008168(methyltransferase activity);GO:0008270(zinc ion binding);GO:0016740(transferase activity);GO:0018024(histone-lysine N-methyltransferase activity);GO:0046872(metal ion binding)
A_24_P2463	NM_133336	WHSC1	NM_133336	Homo sapiens Wolf-Hirschhorn syndrome candidate 1 (WHSC1), transcript variant 9, mRNA [NM_133336]	chr4	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0009653(anatomical structure morphogenesis);GO:0016568(chromatin modification)	GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0005515(protein binding);GO:0008168(methyltransferase activity);GO:0008270(zinc ion binding);GO:0016740(transferase activity);GO:0018024(histone-lysine N-methyltransferase activity);GO:0046872(metal ion binding)
A_24_P253003	NM_004626	WNT11	NM_004626	Homo sapiens wingless-type MMTV integration site family, member 11 (WNT11), mRNA [NM_004626]	chr11	GO:0007165(signal transduction);GO:0007223(Wnt receptor signaling pathway, calcium modulating pathway);GO:0007267(cell-cell signaling);GO:0007275(multicellular organismal development);GO:0009653(anatomical structure morphogenesis)	GO:0005576(extracellular region)	GO:0004871(signal transducer activity)
A_23_P124585	AK096342	ZNF93	AK096342	Homo sapiens cDNA FLJ39023 fis, clone NT2RP7004348, highly similar to ZINC FINGER PROTEIN 93. [AK096342]	chr19	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003676(nucleic acid binding);GO:0003700(transcription factor activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
Significantly Shear-Responsive Genes, 0.01<p<0.05 (ANOVA corrected pForce<0.05; EC paired t-test p<0.05; MSC paired t-test p<0.05) - 474 genes								
A_24_P195454	A_24_P195454	A_24_P195454			chr1			
A_24_P221285	A_24_P221285	A_24_P221285			chrX			
A_24_P221475	A_24_P221475	A_24_P221475			chr7			
A_24_P233560	A_24_P233560	A_24_P233560						
A_24_P50139	A_24_P50139	A_24_P50139			chr17			
A_24_P655888	A_24_P655888	A_24_P655888			chr8			
A_24_P84711	**A_24_P84711**	**A_24_P84711**			**chr7**			
A_32_P128399	A_32_P128399	A_32_P128399			chr2			
A_32_P132169	A_32_P132169	A_32_P132169			chr10			
A_32_P149735	A_32_P149735	A_32_P149735			chr19			
A_32_P157671	A_32_P157671	A_32_P157671			chr17			
A_32_P169243	A_32_P169243	A_32_P169243			chr5			
A_32_P171043	A_32_P171043	A_32_P171043			chr18			
A_32_P196142	A_32_P196142	A_32_P196142			chr18			
A_32_P7521	AA065042	AA065042	AA065042	AA065042 zm12g12.s1 Stratagene pancreas (#937208) Homo sapiens cDNA clone IMAGE:525478 3', mRNA sequence [AA065042]	chr21			
A_23_P158976	NM_000392	ABCC2	NM_000392	Homo sapiens ATP-binding cassette, sub-family C (CFTR/MRP), member 2 (ABCC2), mRNA [NM_000392]	chr10	GO:0006810(transport)	GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0000166(nucleotide binding);GO:0005215(transporter activity);GO:0005524(ATP binding);GO:0008514(organic anion transporter activity);GO:0016887(ATPase activity);GO:0042626(ATPase activity, coupled to transmembrane movement of substances)
A_23_P207507	NM_003786	ABCC3	NM_003786	Homo sapiens ATP-binding cassette, sub-family C (CFTR/MRP), member 3 (ABCC3), mRNA [NM_003786]	chr17	GO:0006810(transport)	GO:0005624(membrane fraction);GO:0005887(integral to plasma membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0000166(nucleotide binding);GO:0005215(transporter activity);GO:0005524(ATP binding);GO:0008514(organic anion transporter activity);GO:0016887(ATPase activity);GO:0042626(ATPase activity, coupled to transmembrane movement of substances)
A_23_P356616	NM_145804	ABTB2	NM_145804	Homo sapiens ankyrin repeat and BTB (POZ) domain containing 2 (ABTB2), mRNA [NM_145804]	chr11	GO:0001558(regulation of cell growth)	GO:0005575(cellular_component)	GO:0003674(molecular_function);GO:0005515(protein binding)
A_23_P103371	NM_052998	ADC	NM_052998	Homo sapiens arginine decarboxylase (ADC), mRNA [NM_052998]	chr1	GO:0006596(polyamine biosynthetic process);GO:0007283(spermatogenesis)	GO:0005575(cellular_component)	GO:0008792(arginine decarboxylase activity);GO:0016829(lyase activity)
A_24_P11462	NM_052998	ADC	NM_052998	Homo sapiens arginine decarboxylase (ADC), mRNA [NM_052998]	chr1	GO:0006596(polyamine biosynthetic process);GO:0007283(spermatogenesis)	GO:0005575(cellular_component)	GO:0008792(arginine decarboxylase activity);GO:0016829(lyase activity)
A_32_P30004	AF086044	AF086044	AF086044	Homo sapiens full length insert cDNA clone YX74D05. [AF086044]	chr12			

A_24_P664918	AF339799	AF339799	AF339799	Homo sapiens clone IMAGE:2363394, mRNA sequence. [AF339799]	chr13			
A_24_P29876	NM_018361	AGPAT5	NM_018361	Homo sapiens 1-acylglycerol-3-phosphate O-acyltransferase 5 (lysophosphatidic acid acyltransferase, epsilon) (AGPAT5), mRNA [NM_018361]	chr8	GO:0008152(metabolic process);GO:0008654(phospholipid biosynthetic process)	GO:0005575(cellular_component);GO:0005739(mitochondrion);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0003841(1-acylglycerol-3-phosphate O-acyltransferase activity);GO:0008415(acyltransferase activity);GO:0016740(transferase activity)
A_24_P817128	AI085037	AI085037	AI085037	AI085037 ow85g07.s1 Soares_fetal_liver_spleen_1NFLS_S1 Homo sapiens cDNA clone IMAGE:1653660 3', mRNA sequence [AI085037]	chr11			
A_23_P102071	AK027315	AK027315	AK027315	Homo sapiens cDNA FLJ14409 fis, clone HEMBA1004408, moderately similar to PEPTIDYL-PROLYL CIS-TRANS ISOMERASE 10 (EC 5.2.1.8). [AK027315]	chr2			
A_23_P303978	AK056230	AK056230	AK056230	Homo sapiens cDNA FLJ31668 fis, clone NT2RI2004916. [AK056230]	chr7			
A_32_P29200	AK093416	AK093416	AK093416	Homo sapiens cDNA FLJ36097 fis, clone TESTI2020956. [AK093416]	chr4			
A_24_P503669	AK093628	AK093628	AK093628	Homo sapiens cDNA FLJ36309 fis, clone THYMU2004986. [AK093628]	chr15			
A_23_P328174	AK097219	AK097219	AK097219	Homo sapiens cDNA FLJ39900 fis, clone SPLEN2017121. [AK097219]	chr17			
A_24_P778844	AK124841	AK124841	AK124841	Homo sapiens cDNA FLJ42851 fis, clone BRHIP2005719. [AK124841]	chr15			
A_24_P563966	AL117454	AL117454	AL117454	Homo sapiens mRNA; cDNA DKFZp586J1717 (from clone DKFZp586J1717). [AL117454]	chr15			
A_24_P937325	AL713762	AL713762	AL713762	Homo sapiens mRNA; cDNA DKFZp434K1572 (from clone DKFZp434K1572). [AL713762]	chr12			
A_23_P207213	NM_000691	ALDH3A1	NM_000691	Homo sapiens aldehyde dehydrogenase 3 family, memberA1 (ALDH3A1), mRNA [NM_000691]	chr17	GO:0006081(aldehyde metabolic process);GO:0006118(electron transport);GO:0008152(metabolic process)	GO:0005783(endoplasmic reticulum);GO:0005829(cytosol)	GO:0004029(aldehyde dehydrogenase (NAD) activity);GO:0004030(aldehyde dehydrogenase [NAD(P)+] activity);GO:0008106(alcohol dehydrogenase (NADP+) activity);GO:0016491(oxidoreductase activity)
A_32_P103309	NM_001013620	ALG10B	NM_001013620	Homo sapiens asparagine-linked glycosylation 10 homolog B (yeast, alpha-1,2-glucosyltransferase) (ALG10B), mRNA [NM_001013620]	chr12		GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0016757(transferase activity, transferring glycosyl groups)
A_23_P49351	NM_015944	AMDHD2	NM_015944	Homo sapiens amidohydrolase domain containing 2 (AMDHD2), mRNA [NM_015944]	chr16	GO:0006044(N-acetylglucosamine metabolic process)		GO:0008448(N-acetylglucosamine-6-phosphate deacetylase activity);GO:0016787(hydrolase activity)
A_23_P60079	NM_001147	ANGPT2	NM_001147	Homo sapiens angiopoietin 2 (ANGPT2), mRNA [NM_001147]	chr8	GO:0001525(angiogenesis);GO:0007165(signal transduction);GO:0007275(multicellular organismal development);GO:0030154(cell differentiation)	GO:0005615(extracellular space)	GO:0005102(receptor binding)
A_23_P159325	NM_139314	ANGPTL4	NM_139314	Homo sapiens angiopoietin-like 4 (ANGPTL4), transcript variant 1, mRNA [NM_139314]	chr19	GO:0001525(angiogenesis);GO:0001666(response to hypoxia);GO:0007165(signal transduction);GO:0007275(multicellular organismal development);GO:0009267(cellular response to starvation);GO:0030154(cell differentiation);GO:0043066(negative regulation of apoptosis);GO:0045766(positive regulation of angiogenesis);GO:0045834(positive regulation of lipid metabolic process);GO:0051005(negative regulation of lipoprotein lipase activity)	GO:0005576(extracellular region);GO:0005615(extracellular space)	GO:0004857(enzyme inhibitor activity);GO:0005102(receptor binding)
A_24_P162485	NM_000037	ANK1	NM_000037	Homo sapiens ankyrin 1, erythrocytic (ANK1), transcript variant 3, mRNA [NM_000037]	chr8	GO:0006887(exocytosis);GO:0007010(cytoskeleton organization and biogenesis);GO:0007165(signal transduction);GO:0045199(maintenance of epithelial cell polarity)	GO:0005886(plasma membrane);GO:0015629(actin cytoskeleton);GO:0016323(basolateral plasma membrane)	GO:0005200(structural constituent of cytoskeleton);GO:0008093(cytoskeletal adaptor activity);GO:0019899(enzyme binding);GO:0030507(spectrin binding)
A_23_P58328	NM_007193	ANXA10	NM_007193	Homo sapiens annexin A10 (ANXA10), mRNA [NM_007193]	chr4		GO:0005739(mitochondrion)	GO:0005509(calcium ion binding);GO:0005544(calcium-dependent phospholipid binding)
A_23_P385295	BC021898	AP1S3	BC021898	Homo sapiens adaptor-related protein complex 1, sigma 3 subunit, mRNA (cDNA clone MGC:17284 IMAGE:4340257), complete cds. [BC021898]	chr2	GO:0006886(intracellular protein transport);GO:0006897(endocytosis)	GO:0005802(trans-Golgi network);GO:0005905(coated pit);GO:0030121(AP-1 adaptor complex);GO:0030662(coated vesicle membrane)	GO:0008565(protein transporter activity)
A_24_P66027	NM_004900	APOBEC3B	NM_004900	Homo sapiens apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B (APOBEC3B), mRNA [NM_004900]	chr22			GO:0008270(zinc ion binding);GO:0016787(hydrolase activity);GO:0016814(hydrolase activity, acting on carbon-nitrogen (but not peptide) bonds, in cyclic amidines)
A_23_P369966	NM_152426	APOBEC3D	NM_152426	Homo sapiens apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3D (putative) (APOBEC3D), mRNA [NM_152426]	chr22			GO:0008270(zinc ion binding);GO:0016787(hydrolase activity);GO:0016814(hydrolase activity, acting on carbon-nitrogen (but not peptide) bonds, in cyclic amidines);GO:0046872(metal ion binding)
A_23_P19894	NM_198098	AQP1	NM_198098	Homo sapiens aquaporin 1 (Colton blood group) (AQP1), mRNA [NM_198098]	chr7	GO:0006810(transport);GO:0006833(water transport);GO:0007588(excretion)	GO:0005887(integral to plasma membrane);GO:0016020(membrane);GO:0016021(integral to membrane);GO:0019867(outer membrane)	GO:0005215(transporter activity);GO:0005372(water transporter activity);GO:0015288(porin activity)
A_23_P372834	NM_198098	AQP1	NM_198098	Homo sapiens aquaporin 1 (Colton blood group) (AQP1), mRNA [NM_198098]	chr7	GO:0006810(transport);GO:0006833(water transport);GO:0007588(excretion)	GO:0005887(integral to plasma membrane);GO:0016020(membrane);GO:0016021(integral to membrane);GO:0019867(outer membrane)	GO:0005215(transporter activity);GO:0005372(water transporter activity);GO:0015288(porin activity)

A_23_P136805	NM_014783	ARHGAP11A	NM_014783	Homo sapiens Rho GTPase activating protein 11A (ARHGAP11A), transcript variant 1, mRNA [NM_014783]	chr15	GO:0007165(signal transduction)	GO:0005622(intracellular)	GO:0005096(GTPase activator activity)
A_24_P296254	NM_014783	ARHGAP11A	NM_014783	Homo sapiens Rho GTPase activating protein 11A (ARHGAP11A), transcript variant 1, mRNA [NM_014783]	chr15	GO:0007165(signal transduction)	GO:0005622(intracellular)	GO:0005096(GTPase activator activity)
A_23_P213298	NM_024590	ARSJ	NM_024590	Homo sapiens arylsulfatase family, member J (ARSJ), mRNA [NM_024590]	chr4	GO:0008152(metabolic process)		GO:0004065(arylsulfatase activity);GO:0005509(calcium ion binding);GO:0016787(hydrolase activity)
A_23_P52017	NM_018136	ASPM	NM_018136	Homo sapiens asp (abnormal spindle) homolog, microcephaly associated (Drosophila) (ASPM), mRNA [NM_018136]	chr1	GO:0007049(cell cycle);GO:0007067(mitosis);GO:0051301(cell division)	GO:0005634(nucleus)	GO:0005516(calmodulin binding)
A_23_P216068	NM_014109	ATAD2	NM_014109	Homo sapiens ATPase family, AAA domain containing 2 (ATAD2), mRNA [NM_014109]	chr8			GO:0000166(nucleotide binding);GO:0005524(ATP binding);GO:0017111(nucleoside-triphosphatase activity)
A_24_P113144	NM_024857	ATAD5	NM_024857	Homo sapiens ATPase family, AAA domain containing 5 (ATAD5), mRNA [NM_024857]	chr17			GO:0000166(nucleotide binding);GO:0005524(ATP binding);GO:0017111(nucleoside-triphosphatase activity)
A_24_P294842	NM_000332	ATXN1	NM_000332	Homo sapiens ataxin 1 (ATXN1), mRNA [NM_000332]	chr6	GO:0008219(cell death)	GO:0005634(nucleus);GO:0005737(cytoplasm);GO:0016363 (nuclear matrix)	GO:0003723(RNA binding);GO:0042802(identical protein binding)
A_23_P131866	NM_198433	AURKA	NM_198433	Homo sapiens aurora kinase A (AURKA), transcript variant 1, mRNA [NM_198433]	chr20	GO:0000278(mitotic cell cycle);GO:0006468(protein amino acid phosphorylation);GO:0007051(spindle organization and biogenesis);GO:0007067(mitosis);GO:0048015(phosphoinositide-mediated signaling)	GO:0005634(nucleus);GO:0005819(spindle)	GO:0000166(nucleotide binding);GO:0004672(protein kinase activity);GO:0004674(protein serine/threonine kinase activity);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0016301(kinase activity);GO:0016740(transferase activity)
A_23_P33511	AX721087	AX721087	AX721087	Sequence 47 from Patent WO0220754. [AX721087]	chr8			
A_32_P221966	AY102069	AY102069	AY102069	Homo sapiens surfactant associated protein F mRNA, partial sequence. [AY102069]	chr10			
A_23_P67771	NM_000465	BARD1	NM_000465	Homo sapiens BRCA1 associated RING domain 1 (BARD1), mRNA [NM_000465]	chr2	GO:0001894(tissue homeostasis);GO:0006974(response to DNA damage stimulus);GO:0007050(cell cycle arrest);GO:0016567(protein ubiquitination);GO:0031441(negative regulation of mRNA 3'-end processing);GO:0042325(regulation of phosphorylation);GO:0043065(positive regulation of apoptosis);GO:0043066(negative regulation of apoptosis);GO:0045732(positive regulation of protein catabolic process);GO:0046826(negative regulation of protein export from nucleus)	GO:0000151(ubiquitin ligase complex);GO:0005622(intracellular);GO:0005634(nucleus); GO:0005737(cytoplasm);GO:0031436(BRCA1-BARD1 complex)	GO:0003723(RNA binding);GO:0004842(ubiquitin-protein ligase activity);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0019900(kinase binding);GO:0042803(protein homodimerization activity);GO:0046872(metal ion binding);GO:0046982(protein heterodimerization activity)
A_23_P370682	NM_138456	BATF2	NM_138456	Homo sapiens basic leucine zipper transcription factor, ATF-like 2 (BATF2), mRNA [NM_138456]	chr11	GO:0006355(regulation of transcription, DNA-dependent)	GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0046983(protein dimerization activity)
A_24_P851522	BC015449	BC015449	BC015449	Homo sapiens, clone IMAGE:4427279, mRNA. [BC015449]	chr8			
A_32_P186364	BC031314	BC031314	BC031314	Homo sapiens cDNA clone IMAGE:5276765. [BC031314]	chr14			
A_32_P114003	BC037827	BC037827	BC037827	Homo sapiens cDNA clone IMAGE:4811567. [BC037827]	chr8			
A_32_P168605	BC039411	BC039411	BC039411	Homo sapiens cDNA clone IMAGE:5301690. [BC039411]	chr4			
A_32_P187651	BC047636	BC047636	BC047636	Homo sapiens cDNA clone IMAGE:4822429. [BC047636]	chr11			
A_24_P378581	BC070125	BC070125	BC070125	Homo sapiens cDNA clone MGC:88103 IMAGE:4693019, complete cds. [BC070125]	chr17			
A_23_P50477	NM_138639	BCL2L12	NM_138639	Homo sapiens BCL2-like 12 (proline rich) (BCL2L12), transcript variant 1, mRNA [NM_138639]	chr19	GO:0006915(apoptosis)		
A_23_P127891	NM_170735	BDNF	NM_170735	Homo sapiens brain-derived neurotrophic factor (BDNF), transcript variant 1, mRNA [NM_170735]	chr11	GO:0001657(ureteric bud development);GO:0006916(anti-apoptosis);GO:0007406(negative regulation of neuroblast proliferation);GO:0007411(axon guidance);GO:0007412(axon target recognition);GO:0007631(feeding behavior);GO:0008038(neuron recognition);GO:0016358(dendrite development);GO:0019222(regulation of metabolic process);GO:0042490(mechanoreceptor differentiation);GO:0045666(positive regulation of neuron differentiation);GO:0046668(regulation of retinal programmed cell death);GO:0048167(regulation of synaptic plasticity)	GO:0016023(cytoplasmic membrane-bound vesicle)	GO:0005515(protein binding);GO:0008083(growth factor activity)
A_32_P71744	BG695979	BG695979	BG695979	602658119F1 NCI_CGAP_Skn3 Homo sapiens cDNA clone IMAGE:4800772 5', mRNA sequence [BG695979]	chr1			

A_23_P118815	NM_001012271	BIRC5	NM_001012271	Homo sapiens baculoviral IAP repeat-containing 5 (survivin) (BIRC5), transcript variant 3, mRNA [NM_001012271]	chr17	GO:0000086(G2/M transition of mitotic cell cycle);GO:0000910(cytokinesis);GO:0006915(apoptosis);GO:0006916(anti-apoptosis);GO:0007049(cell cycle);GO:0007067(mitosis);GO:0031503(protein complex localization);GO:0031536(positive regulation of exit from mitosis);GO:0043154(negative regulation of caspase activity);GO:0045931(positive regulation of progression through mitotic cell cycle);GO:0051303(establishment of chromosome localization)	GO:0000775(chromosome, pericentric region);GO:0005622(intracellular);GO:0005634(nucleus);GO:0005694(chromosome);GO:0005737(cytoplasm);GO:0005814(centriole);GO:0005829(cytosol);GO:0005876(spindle microtubule);GO:0005881(cytoplasmic microtubule);GO:0030496(midbody);GO:0031021(interphase microtubule organizing center);GO:0043234(protein complex)	GO:0004869(cysteine protease inhibitor activity);GO:0008017(microtubule binding);GO:0008270(zinc ion binding);GO:0042803(protein homodimerization activity);GO:0043027(caspase inhibitor activity);GO:0046872(metal ion binding);GO:0046982(protein heterodimerization activity);GO:0048037(cofactor binding)
A_32_P107097	BJ990245	BJ990245	BJ990245	BJ990245 human hepatoblastoma cDNA Homo sapiens cDNA clone hkmt-0791 3', mRNA sequence [BJ990245]	chr2			
A_23_P88630	NM_000057	BLM	NM_000057	Homo sapiens Bloom syndrome (BLM), mRNA [NM_000057]	chr15	GO:0006260(DNA replication);GO:0006281(DNA repair);GO:0006310(DNA recombination);GO:0051098(regulation of binding)	GO:0005622(intracellular);GO:0005634(nucleus);GO:0005657(replication fork)	GO:0000166(nucleotide binding);GO:0003677(DNA binding);GO:0004003(ATP-dependent DNA helicase activity);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0016787(hydrolase activity);GO:0016818(hydrolase activity, acting on acid anhydrides, in phosphorus-containing anhydrides)
A_23_P207400	NM_007295	BRCA1	NM_007295	Homo sapiens breast cancer 1, early onset (BRCA1), transcript variant BRCA1b, mRNA [NM_007295]	chr17	GO:0000075(cell cycle checkpoint);GO:0006281(DNA repair);GO:0006357(regulation of transcription from RNA polymerase II promoter);GO:0006359(regulation of transcription from RNA polymerase III promoter);GO:0006633(fatty acid biosynthetic process);GO:0006978(DNA damage response, signal transduction by p53 class mediator resulting in transcription of p21 class mediator);GO:0007049(cell cycle);GO:0007059(chromosome segregation);GO:0008630(DNA damage response, signal transduction resulting in induction of apoptosis);GO:0016481(negative regulation of transcription);GO:0016567(protein ubiquitination);GO:0030521(androgen receptor signaling pathway);GO:0031398(positive regulation of protein ubiquitination);GO:0042127(regulation of cell proliferation);GO:0042981(regulation of apoptosis);GO:0045717(negative regulation of fatty acid biosynthetic process);GO:0045739(positive regulation of DNA repair);GO:0045786(negative regulation of progression through cell cycle);GO:0045893(positive regulation of transcription, DNA-dependent);GO:0046600(negative regulation of centriole replication)	GO:0000151(ubiquitin ligase complex);GO:0005575(cellular_component);GO:0005622(intracellular);GO:0005634(nucleus);GO:0008274(gamma-tubulin ring complex);GO:0031436(BRCA1-BARD1 complex)	GO:0003674(molecular_function);GO:0003677(DNA binding);GO:0003713(transcription coactivator activity);GO:0004842(ubiquitin-protein ligase activity);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0015631(tubulin binding);GO:0019899(enzyme binding);GO:0046872(metal ion binding);GO:0050681(androgen receptor binding)
A_23_P124417	NM_004336	BUB1	NM_004336	Homo sapiens BUB1 budding uninhibited by benzimidazoles 1 homolog (yeast) (BUB1), mRNA [NM_004336]	chr2	GO:0006468(protein amino acid phosphorylation);GO:0007049(cell cycle);GO:0007067(mitosis);GO:0007094(mitotic spindle checkpoint);GO:0008283(cell proliferation);GO:0051301(cell division)	GO:0000776(kinetochore);GO:0005634(nucleus);GO:0005816(spindle pole body)	GO:0000166(nucleotide binding);GO:0004674(protein serine/threonine kinase activity);GO:0005524(ATP binding);GO:0016740(transferase activity)
A_32_P27135	BX538139	BX538139	BX538139	Homo sapiens mRNA; cDNA DKFZp686L21117 (from clone DKFZp686L21117) [BX538139]	chr13			
A_23_P87773	NM_017915	C12orf48	NM_017915	Homo sapiens chromosome 12 open reading frame 48 (C12orf48), mRNA [NM_017915]	chr12		GO:0005634(nucleus)	GO:0003677(DNA binding)
A_24_P90597	NM_032849	C13orf33	NM_032849	Homo sapiens chromosome 13 open reading frame 33 (C13orf33), mRNA [NM_032849]	chr13			
A_23_P25626	NM_024808	C13orf34	NM_024808	Homo sapiens chromosome 13 open reading frame 34 (C13orf34), mRNA [NM_024808]	chr13	GO:0007049(cell cycle);GO:0007067(mitosis);GO:0051301(cell division)		
A_23_P430201	NM_152446	C14orf145	NM_152446	Homo sapiens chromosome 14 open reading frame 145 (C14orf145), mRNA [NM_152446]	chr14			
A_23_P140705	BC004543	C15orf23	BC004543	Homo sapiens chromosome 15 open reading frame 23, mRNA (cDNA clone IMAGE:3952251), partial cds. [BC004543]	chr15		GO:0005634(nucleus)	GO:0005515(protein binding)
A_24_P942335	BC002881	C15orf42	BC002881	Homo sapiens chromosome 15 open reading frame 42, mRNA (cDNA clone IMAGE:3940845), partial cds. [BC002881]	chr15			GO:0004308(exo-alpha-sialidase activity)
A_32_P109296	NM_152259	C15orf42	NM_152259	Homo sapiens chromosome 15 open reading frame 42 (C15orf42), mRNA [NM_152259]	chr15			GO:0004308(exo-alpha-sialidase activity)
A_24_P48248	NM_024032	C17orf53	NM_024032	Homo sapiens chromosome 17 open reading frame 53 (C17orf53), mRNA [NM_024032]	chr17			
A_23_P164814	NM_024323	C19orf57	NM_024323	Homo sapiens chromosome 19 open reading frame 57 (C19orf57), mRNA [NM_024323]	chr19	GO:0007275(multicellular organismal development)	GO:0005575(cellular_component)	GO:0003674(molecular_function);GO:0005515(protein binding)

A_24_P922808	BC020640	C1orf121	BC020640	Homo sapiens chromosome 1 open reading frame 121, mRNA (cDNA clone IMAGE:4718788), partial cds. [BC020640]	chr1			
A_24_P221903	AL117578	C21orf30	AL117578	Homo sapiens mRNA; cDNA DKFZp434C128 (from clone DKFZp434C128). [AL117578]	chr21			
A_23_P252335	NM_018944	C21orf45	NM_018944	Homo sapiens chromosome 21 open reading frame 45 (C21orf45), mRNA [NM_018944]	chr21	GO:0008150(biological_process)	GO:0005575(cellular_component)	GO:0003674(molecular_function)
A_32_P137926	NM_198468	C6orf167	NM_198468	Homo sapiens chromosome 6 open reading frame 167 (C6orf167), mRNA [NM_198468]	chr6			GO:0005515(protein binding)
A_32_P143245	NM_001012507	C6orf173	NM_001012507	Homo sapiens chromosome 6 open reading frame 173 (C6orf173), mRNA [NM_001012507]	chr6		GO:0005634(nucleus)	
A_23_P133854	NM_001007531	C6orf194	NM_001007531	Homo sapiens chromosome 6 open reading frame 194 (C6orf194), mRNA [NM_001007531]	chr6			
A_23_P215675	NM_018224	C7orf44	NM_018224	Homo sapiens chromosome 7 open reading frame 44 (C7orf44), mRNA [NM_018224]	chr7		GO:0016020(membrane);GO:0016021(integral to membrane)	
A_23_P216517	NM_032818	C9orf100	NM_032818	Homo sapiens chromosome 9 open reading frame 100 (C9orf100), mRNA [NM_032818]	chr9	GO:0035023(regulation of Rho protein signal transduction)	GO:0005622(intracellular)	GO:0005085(guanyl-nucleotide exchange factor activity);GO:0005089(Rho guanyl-nucleotide exchange factor activity)
A_23_P422851	NM_138375	CABLES1	NM_138375	Homo sapiens Cdk5 and Abl enzyme substrate 1 (CABLES1), mRNA [NM_138375]	chr18	GO:0007049(cell cycle);GO:0007399(nervous system development);GO:0051302(regulation of cell division)	GO:0005634(nucleus)	GO:0005515(protein binding);GO:0016538(cyclin-dependent protein kinase regulator activity)
A_24_P190190	NM_000723	CACNB1	NM_000723	Homo sapiens calcium channel, voltage-dependent, beta 1 subunit (CACNB1), transcript variant 1, mRNA [NM_000723]	chr17	GO:0006811(ion transport);GO:0006816(calcium ion transport);GO:0006936(muscle contraction)	GO:0005624(membrane fraction);GO:0005891(voltage-gated calcium channel complex)	GO:0005245(voltage-gated calcium channel activity);GO:0005509(calcium ion binding)
A_24_P940678	NM_170589	CASC5	NM_170589	Homo sapiens cancer susceptibility candidate 5 (CASC5), transcript variant 1, mRNA [NM_170589]	chr15	GO:0001675(acrosome formation)	GO:0001669(acrosome);GO:0005634(nucleus)	GO:0005515(protein binding)
A_24_P12626	NM_001753	CAV1	NM_001753	Homo sapiens caveolin 1, caveolae protein, 22kDa (CAV1), mRNA [NM_001753]	chr7	GO:0000188(inactivation of MAPK activity);GO:0001937(negative regulation of endothelial cell proliferation);GO:0006641(triacylglycerol metabolic process);GO:0009968(negative regulation of signal transduction);GO:0019217(regulation of fatty acid metabolic process);GO:0019915(sequestering of lipid);GO:0030301(cholesterol transport);GO:0042632(cholesterol homeostasis);GO:0045019(negative regulation of nitric oxide biosynthetic process);GO:0045907(positive regulation of vasoconstriction);GO:0045908(negative regulation of vasodilation);GO:0051260(protein homooligomerization)	GO:0000139(Golgi membrane);GO:0000299(integral to membrane of membrane fraction);GO:0005783(endoplasmic reticulum);GO:0005886(plasma membrane);GO:0005887(integral to plasma membrane);GO:0016021(integral to membrane);GO:0016599(caveolar membrane);GO:0045121(lipid raft);GO:0048471(perinuclear region of cytoplasm)	GO:0005198(structural molecule activity);GO:0005515(protein binding);GO:0015485(cholesterol binding)
A_24_P251599	NM_001234	CAV3	NM_001234	Homo sapiens caveolin 3 (CAV3), transcript variant 2, mRNA [NM_001234]	chr3	GO:0007517(muscle development)	GO:0005624(membrane fraction);GO:0016010(dystrophin-associated glycoprotein complex);GO:0016020(membrane);GO:0016021(integral to membrane);GO:0016599(caveolar membrane)	GO:0005515(protein binding)
A_32_P104407	CB243784	CB243784	CB243784	CB243784 UI-CF-FN0-agf-p-18-0-UI.s1 UI-CF-FN0 Homo sapiens cDNA clone UI-CF-FN0-agf-p-18-0-UI 3', mRNA sequence [CB243784]	chr1			
A_23_P2355	NM_012117	CBX5	NM_012117	Homo sapiens chromobox homolog 5 (HP1 alpha homolog, Drosophila) (CBX5), mRNA [NM_012117]	chr12	GO:0006333(chromatin assembly or disassembly)	GO:0000776(kinetochore);GO:0000785(chromatin);GO:0005634(nucleus);GO:0005635(nuclear envelope);GO:0005720(nuclear heterochromatin)	GO:0003682(chromatin binding);GO:0005515(protein binding)
A_23_P55544	NM_133459	CCBE1	NM_133459	Homo sapiens collagen and calcium binding EGF domains 1 (CCBE1), mRNA [NM_133459]	chr18	GO:0006817(phosphate transport)	GO:0005737(cytoplasm)	GO:0005509(calcium ion binding)
A_23_P155106	NM_024821	CCDC134	NM_024821	Homo sapiens coiled-coil domain containing 134 (CCDC134), mRNA [NM_024821]	chr22			
A_24_P195831	NM_030771	CCDC34	NM_030771	Homo sapiens coiled-coil domain containing 34 (CCDC34), transcript variant 1, mRNA [NM_030771]	chr11			
A_23_P41948	NM_017785	CCDC99	NM_017785	Homo sapiens coiled-coil domain containing 99 (CCDC99), mRNA [NM_017785]	chr5			
A_23_P60227	NM_005893	CCIN	NM_005893	Homo sapiens calicin (CCIN), mRNA [NM_005893]	chr9	GO:0007275(multicellular organismal development);GO:0007283(spermatogenesis);GO:0030154(cell differentiation)	GO:0005856(cytoskeleton)	GO:0005200(structural constituent of cytoskeleton);GO:0005515(protein binding)
A_23_P122197	NM_031966	CCNB1	NM_031966	Homo sapiens cyclin B1 (CCNB1), mRNA [NM_031966]	chr5	GO:0000074(regulation of progression through cell cycle);GO:0000086(G2/M transition of mitotic cell cycle);GO:0007049(cell cycle);GO:0007067(mitosis);GO:0051301(cell division)	GO:0005575(cellular_component);GO:0005634(nucleus)	GO:0005515(protein binding)
A_23_P65757	NM_004701	CCNB2	NM_004701	Homo sapiens cyclin B2 (CCNB2), mRNA [NM_004701]	chr15	GO:0000074(regulation of progression through cell cycle);GO:0007049(cell cycle);GO:0007067(mitosis);GO:0051301(cell division)	GO:0005634(nucleus);GO:0015630(microtubule cytoskeleton)	GO:0005515(protein binding)

A_23_P215976	NM_057749	CCNE2	NM_057749	Homo sapiens cyclin E2 (CCNE2), transcript variant 1, mRNA [NM_057749]	chr8	GO:0000074(regulation of progression through cell cycle);GO:0000075(cell cycle checkpoint);GO:0000079(regulation of cyclin-dependent protein kinase activity);GO:0006270(DNA replication initiation);GO:0007049(cell cycle);GO:0051301(cell division)	GO:0005634(nucleus)	GO:0005515(protein binding);GO:0016538(cyclin-dependent protein kinase regulator activity)
A_32_P220798	NM_001773	CD34	NM_001773	Homo sapiens CD34 molecule (CD34), transcript variant 2, mRNA [NM_001773]	chr1	GO:0007155(cell adhesion);GO:0016337(cell-cell adhesion);GO:0050900(leukocyte migration)	GO:0009897(external side of plasma membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005515(protein binding);GO:0030246(carbohydrate binding)
A_32_P44916	CD619445	CD619445	CD619445	CD619445 56049167H1 FLP Homo sapiens cDNA, mRNA sequence [CD619445]	chr14			
A_23_P210811	NM_012072	CD93	NM_012072	Homo sapiens CD93 molecule (CD93), mRNA [NM_012072]	chr20	GO:0006909(phagocytosis);GO:0016337(cell-cell adhesion);GO:0042116(macrophage activation)	GO:0005886(plasma membrane);GO:0016021(integral to membrane);GO:0016023(cytoplasmic membrane-bound vesicle)	GO:0001849(complement component C1q binding);GO:0004872(receptor activity);GO:0005509(calcium ion binding);GO:0005515(protein binding);GO:0005529(sugar binding)
A_23_P57379	NM_003504	CDC45L	NM_003504	Homo sapiens CDC45 cell division cycle 45-like (S. cerevisiae) (CDC45L), mRNA [NM_003504]	chr22	GO:0000074(regulation of progression through cell cycle);GO:0000076(DNA replication checkpoint);GO:0006260(DNA replication);GO:0006270(DNA replication initiation);GO:0007049(cell cycle)	GO:0005634(nucleus)	GO:0005515(protein binding)
A_23_P385861	NM_152562	CDCA2	NM_152562	Homo sapiens cell division cycle associated 2 (CDCA2), mRNA [NM_152562]	chr8			
A_23_P104651	NM_080668	CDCA5	NM_080668	Homo sapiens cell division cycle associated 5 (CDCA5), mRNA [NM_080668]	chr11	GO:0000082(G1/S transition of mitotic cell cycle);GO:0007049(cell cycle);GO:0007067(mitosis);GO:0007076(mitotic chromosome condensation);GO:0007080(mitotic metaphase plate congression);GO:0051301(cell division)	GO:0005634(nucleus);GO:0005737(cytoplasm);GO:0008278(cohesin complex)	GO:0003682(chromatin binding);GO:0005515(protein binding)
A_24_P171549	NM_031942	CDCA7	NM_031942	Homo sapiens cell division cycle associated 7 (CDCA7), transcript variant 1, mRNA [NM_031942]	chr2	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0042127(regulation of cell proliferation)	GO:0005634(nucleus)	
A_24_P274795	NM_018719	CDCA7L	NM_018719	Homo sapiens cell division cycle associated 7-like (CDCA7L), mRNA [NM_018719]	chr7	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent)	GO:0005634(nucleus)	
A_23_P375	NM_018101	CDCA8	NM_018101	Homo sapiens cell division cycle associated 8 (CDCA8), mRNA [NM_018101]	chr1	GO:0007049(cell cycle);GO:0007067(mitosis);GO:0051301(cell division)	GO:0000775(chromosome, pericentric region);GO:0005634(nucleus);GO:0005694(chromosome);GO:0043234(protein complex)	GO:0005515(protein binding)
A_23_P144656	NM_006727	CDH10	NM_006727	Homo sapiens cadherin 10, type 2 (T2-cadherin) (CDH10), mRNA [NM_006727]	chr5	GO:0007156(homophilic cell adhesion)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005509(calcium ion binding);GO:0005515(protein binding)
A_23_P28999	AK025855	CDH4	AK025855	Homo sapiens cDNA: FLJ22202 fis, clone HRC01333. [AK025855]	chr20	GO:0007155(cell adhesion);GO:0007156(homophilic cell adhesion);GO:0007411(axon guidance);GO:0045773(positive regulation of axon extension)	GO:0005886(plasma membrane);GO:0016021(integral to membrane)	GO:0005509(calcium ion binding);GO:0005515(protein binding)
A_23_P85460	NM_001262	CDKN2C	NM_001262	Homo sapiens cyclin-dependent kinase inhibitor 2C (p18, inhibits CDK4) (CDKN2C), transcript variant 1, mRNA [NM_001262]	chr1	GO:0007049(cell cycle);GO:0007050(cell cycle arrest);GO:0008285(negative regulation of cell proliferation)	GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0004861(cyclin-dependent protein kinase inhibitor activity);GO:0005515(protein binding)
A_23_P48669	NM_005192	CDKN3	NM_005192	Homo sapiens cyclin-dependent kinase inhibitor 3 (CDK2-associated dual specificity phosphatase) (CDKN3), mRNA [NM_005192]	chr14	GO:0000079(regulation of cyclin-dependent protein kinase activity);GO:0000082(G1/S transition of mitotic cell cycle);GO:0007049(cell cycle);GO:0007050(cell cycle arrest);GO:0008285(negative regulation of cell proliferation);GO:0016311(dephosphorylation)		GO:0004725(protein tyrosine phosphatase activity);GO:0005515(protein binding);GO:0008138(protein tyrosine/serine/threonine phosphatase activity);GO:0016787(hydrolase activity)
A_23_P37704	NM_030928	CDT1	NM_030928	Homo sapiens chromatin licensing and DNA replication factor 1 (CDT1), mRNA [NM_030928]	chr16	GO:0000076(DNA replication checkpoint);GO:0006260(DNA replication);GO:0007049(cell cycle);GO:0007090(regulation of S phase of mitotic cell cycle);GO:0030174(regulation of DNA replication initiation)	GO:0005634(nucleus);GO:0005657(replication fork)	GO:0003677(DNA binding);GO:0005515(protein binding)
A_24_P176374	NM_030928	CDT1	NM_030928	Homo sapiens chromatin licensing and DNA replication factor 1 (CDT1), mRNA [NM_030928]	chr16	GO:0000076(DNA replication checkpoint);GO:0006260(DNA replication);GO:0007049(cell cycle);GO:0007090(regulation of S phase of mitotic cell cycle);GO:0030174(regulation of DNA replication initiation)	GO:0005634(nucleus);GO:0005657(replication fork)	GO:0003677(DNA binding);GO:0005515(protein binding)
A_24_P413884	NM_001809	CENPA	NM_001809	Homo sapiens centromere protein A (CENPA), transcript variant 1, mRNA [NM_001809]	chr2	GO:0006334(nucleosome assembly);GO:0007001(chromosome organization and biogenesis (sensu Eukaryota))	GO:0000775(chromosome, pericentric region);GO:0000786(nucleosome);GO:0005634(nucleus);GO:0005694(chromosome)	GO:0003677(DNA binding);GO:0003682(chromatin binding)
A_23_P110802	NM_022909	CENPH	NM_022909	Homo sapiens centromere protein H (CENPH), mRNA [NM_022909]	chr5	GO:0051383(kinetochore organization and biogenesis)	GO:0000776(kinetochore);GO:0005634(nucleus);GO:0005694(chromosome)	GO:0005515(protein binding)
A_23_P252292	NM_006733	CENPI	NM_006733	Homo sapiens centromere protein I (CENPI), mRNA [NM_006733]	chrX	GO:0007283(spermatogenesis);GO:0007292(female gamete generation);GO:0007548(sex differentiation)	GO:0000775(chromosome, pericentric region);GO:0005634(nucleus);GO:0005694(chromosome)	
A_24_P419132	NM_006733	CENPI	NM_006733	Homo sapiens centromere protein I (CENPI), mRNA [NM_006733]	chrX	GO:0007283(spermatogenesis);GO:0007292(female gamete generation);GO:0007548(sex differentiation)	GO:0000775(chromosome, pericentric region);GO:0005634(nucleus);GO:0005694(chromosome)	
A_23_P126120	NM_033319	CENPL	NM_033319	Homo sapiens centromere protein L (CENPL), mRNA [NM_033319]	chr1		GO:0000775(chromosome, pericentric region);GO:0005634(nucleus);GO:0005694(chromosome)	

A_24_P399888	NM_001002876	CENPM	NM_001002876	Homo sapiens centromere protein M (CENPM), transcript variant 2, mRNA [NM_001002876]	chr22		GO:0000775(chromosome, pericentric region);GO:0005634(nucleus);GO:0005694(chromosome)	
A_32_P119174	NM_001012267	CENPP	NM_001012267	Homo sapiens centromere protein P (CENPP), mRNA [NM_001012267]	chr9		GO:0000775(chromosome, pericentric region);GO:0005634(nucleus);GO:0005694(chromosome)	
A_23_P70328	NM_018132	CENPQ	NM_018132	Homo sapiens centromere protein Q (CENPQ), mRNA [NM_018132]	chr6		GO:0000775(chromosome, pericentric region);GO:0005634(nucleus);GO:0005694(chromosome)	
A_23_P43580	NM_007018	CEP110	NM_007018	Homo sapiens centrosomal protein 110kDa (CEP110), mRNA [NM_007018]	chr9		GO:0005634(nucleus);GO:0005813(centrosome)	GO:0003702(RNA polymerase II transcription factor activity);GO:0005515(protein binding)
A_32_P194264	NM_001008708	CHAC2	NM_001008708	Homo sapiens ChaC, cation transport regulator homolog 2 (E. coli) (CHAC2), mRNA [NM_001008708]	chr2			
A_23_P134835	NM_018371	ChGn	NM_018371	Homo sapiens chondroitin beta1,4 N-acetylgalactosaminyltransferase (ChGn), mRNA [NM_018371]	chr8	GO:0007399(nervous system development);GO:0008037(cell recognition);GO:0008283(cell proliferation);GO:0009653(anatomical structure morphogenesis);GO:0015014(heparan sulfate proteoglycan biosynthetic process, polysaccharide chain biosynthetic process);GO:0019276(UDP-N-acetylgalactosamine metabolic process);GO:0030198(extracellular matrix organization and biogenesis);GO:0030206(chondroitin sulfate biosynthetic process);GO:0030210(heparin biosynthetic process);GO:0046398(UDP-glucuronate metabolic process);GO:0050652(dermatan sulfate proteoglycan biosynthetic process, polysaccharide chain biosynthetic process);GO:0050653(chondroitin sulfate proteoglycan biosynthetic process, polysaccharide chain biosynthetic process)	GO:0005622(intracellular);GO:0005625(soluble fraction);GO:0016020(membrane);GO:0016021(integral to membrane);GO:0030173(integral to Golgi membrane)	GO:0005515(protein binding);GO:0008955(peptidoglycan glycosyltransferase activity);GO:0015020(glucuronosyltransferase activity);GO:0016740(transferase activity);GO:0046872(metal ion binding);GO:0047237(glucuronylgalactosylproteoglycan 4-beta-N-acetylgalactosaminyltransferase activity);GO:0047238(glucuronosyl-N-acetylgalactosaminyl-proteoglycan 4-beta-N-acetylgalactosaminyltransferase activity)
A_24_P406525	NM_018371	ChGn	NM_018371	Homo sapiens chondroitin beta1,4 N-acetylgalactosaminyltransferase (ChGn), mRNA [NM_018371]	chr8	GO:0007399(nervous system development);GO:0008037(cell recognition);GO:0008283(cell proliferation);GO:0009653(anatomical structure morphogenesis);GO:0015014(heparan sulfate proteoglycan biosynthetic process, polysaccharide chain biosynthetic process);GO:0019276(UDP-N-acetylgalactosamine metabolic process);GO:0030198(extracellular matrix organization and biogenesis);GO:0030206(chondroitin sulfate biosynthetic process);GO:0030210(heparin biosynthetic process);GO:0046398(UDP-glucuronate metabolic process);GO:0050652(dermatan sulfate proteoglycan biosynthetic process, polysaccharide chain biosynthetic process);GO:0050653(chondroitin sulfate proteoglycan biosynthetic process, polysaccharide chain biosynthetic process)	GO:0005622(intracellular);GO:0005625(soluble fraction);GO:0016020(membrane);GO:0016021(integral to membrane);GO:0030173(integral to Golgi membrane)	GO:0005515(protein binding);GO:0008955(peptidoglycan glycosyltransferase activity);GO:0015020(glucuronosyltransferase activity);GO:0016740(transferase activity);GO:0046872(metal ion binding);GO:0047237(glucuronylgalactosylproteoglycan 4-beta-N-acetylgalactosaminyltransferase activity);GO:0047238(glucuronosyl-N-acetylgalactosaminyl-proteoglycan 4-beta-N-acetylgalactosaminyltransferase activity)
A_23_P420551	NM_007174	CIT	NM_007174	Homo sapiens citron (rho-interacting, serine/threonine kinase 21) (CIT), mRNA [NM_007174]	chr12	GO:0006468(protein amino acid phosphorylation);GO:0007049(cell cycle);GO:0007067(mitosis);GO:0007242(intracellular signaling cascade);GO:0007275(multicellular organismal development);GO:0007399(nervous system development);GO:0030154(cell differentiation);GO:0051301(cell division)		GO:0000166(nucleotide binding);GO:0004674(protein serine/threonine kinase activity);GO:0005083(small GTPase regulator activity);GO:0005524(ATP binding);GO:0008270(zinc ion binding);GO:0016740(transferase activity);GO:0019992(diacylglycerol binding);GO:0046872(metal ion binding)
A_23_P151405	NM_018204	CKAP2	NM_018204	Homo sapiens cytoskeleton associated protein 2 (CKAP2), mRNA [NM_018204]	chr13	GO:0006915(apoptosis);GO:0007049(cell cycle)	GO:0005874(microtubule)	
A_23_P45917	NM_001826	CKS1B	NM_001826	Homo sapiens CDC28 protein kinase regulatory subunit 1B (CKS1B), mRNA [NM_001826]	chr1	GO:0000079(regulation of cyclin-dependent protein kinase activity);GO:0007049(cell cycle);GO:0008283(cell proliferation);GO:0051301(cell division)		GO:0005515(protein binding);GO:0016301(kinase activity);GO:0016538(cyclin-dependent protein kinase regulator activity)
A_32_P192430	NM_001826	CKS1B	NM_001826	Homo sapiens CDC28 protein kinase regulatory subunit 1B (CKS1B), mRNA [NM_001826]	chr1	GO:0000079(regulation of cyclin-dependent protein kinase activity);GO:0007049(cell cycle);GO:0008283(cell proliferation);GO:0051301(cell division)		GO:0005515(protein binding);GO:0016301(kinase activity);GO:0016538(cyclin-dependent protein kinase regulator activity)
A_23_P29800	NM_005602	CLDN11	NM_005602	Homo sapiens claudin 11 (oligodendrocyte transmembrane protein) (CLDN11), mRNA [NM_005602]	chr3	GO:0007155(cell adhesion);GO:0007283(spermatogenesis);GO:0008366(axon ensheathment);GO:0016338(calcium-independent cell-cell adhesion)	GO:0005923(tight junction);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005198(structural molecule activity);GO:0042802(identical protein binding)
A_23_P405088	NM_005602	CLDN11	NM_005602	Homo sapiens claudin 11 (oligodendrocyte transmembrane protein) (CLDN11), mRNA [NM_005602]	chr3	GO:0007155(cell adhesion);GO:0007283(spermatogenesis);GO:0008366(axon ensheathment);GO:0016338(calcium-independent cell-cell adhesion)	GO:0005923(tight junction);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005198(structural molecule activity);GO:0042802(identical protein binding)
A_23_P91512	NM_144492	CLDN14	NM_144492	Homo sapiens claudin 14 (CLDN14), transcript variant 1, mRNA [NM_144492]	chr21	GO:0006461(protein complex assembly);GO:0007605(sensory perception of sound);GO:0016338(calcium-independent cell-cell adhesion)	GO:0005923(tight junction);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005198(structural molecule activity);GO:0042802(identical protein binding)
A_23_P65240	NM_001845	COL4A1	NM_001845	Homo sapiens collagen, type IV, alpha 1 (COL4A1), mRNA [NM_001845]	chr13	GO:0006817(phosphate transport)	GO:0005576(extracellular region);GO:0005581(collagen);GO:0005604(basement membrane);GO:0005737(cytoplasm)	GO:0005201(extracellular matrix structural constituent)
A_23_P205031	NM_001846	COL4A2	NM_001846	Homo sapiens collagen, type IV, alpha 2 (COL4A2), mRNA [NM_001846]	chr13	GO:0006817(phosphate transport);GO:0016525(negative regulation of angiogenesis);GO:0030198(extracellular matrix organization and biogenesis)	GO:0005581(collagen);GO:0005587(collagen type IV);GO:0005737(cytoplasm)	GO:0005201(extracellular matrix structural constituent)

A_24_P365975	NM_005202	COL8A2	NM_005202	Homo sapiens collagen, type VIII, alpha 2 (COL8A2), mRNA [NM_005202]	chr1	GO:0006817(phosphate transport);GO:0016337(cell-cell adhesion);GO:0030198(extracellular matrix organization and biogenesis)	GO:0005604(basement membrane);GO:0005737(cytoplasm)	GO:0005201(extracellular matrix structural constituent);GO:0030674(protein binding, bridging)
A_23_P90436	NM_000095	COMP	NM_000095	Homo sapiens cartilage oligomeric matrix protein (COMP), mRNA [NM_000095]	chr19	GO:0001501(skeletal development);GO:0007155(cell adhesion);GO:0009887(organ morphogenesis)	GO:0005576(extracellular region);GO:0005578(proteinaceous extracellular matrix)	GO:0005201(extracellular matrix structural constituent);GO:0005509(calcium ion binding);GO:0005515(protein binding)
A_24_P264943	NM_000095	COMP	NM_000095	Homo sapiens cartilage oligomeric matrix protein (COMP), mRNA [NM_000095]	chr19	GO:0001501(skeletal development);GO:0007155(cell adhesion);GO:0009887(organ morphogenesis)	GO:0005576(extracellular region);GO:0005578(proteinaceous extracellular matrix)	GO:0005201(extracellular matrix structural constituent);GO:0005509(calcium ion binding);GO:0005515(protein binding)
A_23_P124733	NM_015697	COQ2	NM_015697	Homo sapiens coenzyme Q2 homolog, prenyltransferase (yeast) (COQ2), mRNA [NM_015697]	chr4	GO:0006071(glycerol metabolic process);GO:0006744(ubiquinone biosynthetic process);GO:0008299(isoprenoid biosynthetic process);GO:0009058(biosynthetic process)	GO:0005739(mitochondrion);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0004659(prenyltransferase activity);GO:0016740(transferase activity)
A_23_P107322	NM_032854	CORO6	NM_032854	Homo sapiens coronin 6 (CORO6), mRNA [NM_032854]	chr17			
A_23_P67198	NM_015692	CPAMD8	NM_015692	Homo sapiens C3 and PZP-like, alpha-2-macroglobulin domain containing 8 (CPAMD8), mRNA [NM_015692]	chr19			GO:0004866(endopeptidase inhibitor activity)
A_23_P132738	NM_017541	CRYGS	NM_017541	Homo sapiens crystallin, gamma S (CRYGS), mRNA [NM_017541]	chr3			GO:0005212(structural constituent of eye lens)
A_24_P414205	NM_017541	CRYGS	NM_017541	Homo sapiens crystallin, gamma S (CRYGS), mRNA [NM_017541]	chr3			GO:0005212(structural constituent of eye lens)
A_23_P17393	NM_001316	CSE1L	NM_001316	Homo sapiens CSE1 chromosome segregation 1-like (yeast) (CSE1L), mRNA [NM_001316]	chr20	GO:0000059(protein import into nucleus, docking);GO:0006886(intracellular protein transport);GO:0006915(apoptosis);GO:0008283(cell proliferation)	GO:0005634(nucleus);GO:0005643(nuclear pore);GO:0005737(cytoplasm)	GO:0005488(binding);GO:0008262(importin-alpha export receptor activity);GO:0008565(protein transporter activity)
A_23_P1552	NM_001814	CTSC	NM_001814	Homo sapiens cathepsin C (CTSC), transcript variant 1, mRNA [NM_001814]	chr11	GO:0006508(proteolysis);GO:0006955(immune response)	GO:0005764(lysosome)	GO:0004197(cysteine-type endopeptidase activity);GO:0004214(dipeptidyl-peptidase I activity);GO:0008234(cysteine-type peptidase activity);GO:0031404(chloride ion binding)
A_24_P115762	NM_148170	CTSC	NM_148170	Homo sapiens cathepsin C (CTSC), transcript variant 2, mRNA [NM_148170]	chr11	GO:0006508(proteolysis);GO:0006955(immune response)	GO:0005764(lysosome)	GO:0004197(cysteine-type endopeptidase activity);GO:0004214(dipeptidyl-peptidase I activity);GO:0008234(cysteine-type peptidase activity);GO:0031404(chloride ion binding)
A_23_P115645	NM_006561	CUGBP2	NM_006561	Homo sapiens CUG triplet repeat, RNA binding protein 2 (CUGBP2), transcript variant 2, mRNA [NM_006561]	chr10	GO:0006396(RNA processing);GO:0007528(neuromuscular junction development);GO:0008016(regulation of heart contraction)		GO:0000166(nucleotide binding);GO:0003723(RNA binding)
A_23_P20328	CX165016	CX165016	CX165016	HESC2_23_G02.g1_A035 NIH_MGC_258 Homo sapiens cDNA clone IMAGE:7468613 5', mRNA sequence [CX165016]	chr8			
A_23_P7144	NM_001511	CXCL1	NM_001511	Homo sapiens chemokine (C-X-C motif) ligand 1 (melanoma growth stimulating activity, alpha) (CXCL1), mRNA [NM_001511]	chr4	GO:0006935(chemotaxis);GO:0006954(inflammatory response);GO:0006955(immune response);GO:0007186(G-protein coupled receptor protein signaling pathway);GO:0007242(intracellular signaling cascade);GO:0007399(nervous system development);GO:0008283(cell proliferation);GO:0008285(negative regulation of cell proliferation);GO:0030036(actin cytoskeleton organization and biogenesis)	GO:0005576(extracellular region);GO:0005615(extracellular space)	GO:0008009(chemokine activity);GO:0008047(enzyme activator activity);GO:0008083(growth factor activity)
A_23_P155755	NM_002993	CXCL6	NM_002993	Homo sapiens chemokine (C-X-C motif) ligand 6 (granulocyte chemotactic protein 2) (CXCL6), mRNA [NM_002993]	chr4	GO:0006278(RNA-dependent DNA replication);GO:0006935(chemotaxis);GO:0006954(inflammatory response);GO:0006955(immune response);GO:0007165(signal transduction);GO:0007267(cell-cell signaling)	GO:0005575(cellular_component);GO:0005576(extracellular region);GO:0005615(extracellular space)	GO:0003964(RNA-directed DNA polymerase activity);GO:0008009(chemokine activity);GO:0008201(heparin binding)
A_23_P131676	NM_020311	CXCR7	NM_020311	Homo sapiens chemokine (C-X-C motif) receptor 7 (CXCR7), transcript variant 2, mRNA [NM_020311]	chr2	GO:0007165(signal transduction);GO:0007186(G-protein coupled receptor protein signaling pathway);GO:0008150(biological_process)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0001584(rhodopsin-like receptor activity);GO:0004872(receptor activity)
A_23_P53198	NM_032564	DGAT2	NM_032564	Homo sapiens diacylglycerol O-acyltransferase homolog 2 (mouse) (DGAT2), mRNA [NM_032564]	chr11	GO:0006071(glycerol metabolic process);GO:0006629(lipid metabolic process);GO:0008610(lipid biosynthetic process);GO:0019432(triacylglycerol biosynthetic process)	GO:0005624(membrane fraction);GO:0005783(endoplasmic reticulum);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0004144(diacylglycerol O-acyltransferase activity);GO:0008415(acyltransferase activity);GO:0016740(transferase activity)
A_24_P295791	NM_032564	DGAT2	NM_032564	Homo sapiens diacylglycerol O-acyltransferase homolog 2 (mouse) (DGAT2), mRNA [NM_032564]	chr11	GO:0006071(glycerol metabolic process);GO:0006629(lipid metabolic process);GO:0008610(lipid biosynthetic process);GO:0019432(triacylglycerol biosynthetic process)	GO:0005624(membrane fraction);GO:0005783(endoplasmic reticulum);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0004144(diacylglycerol O-acyltransferase activity);GO:0008415(acyltransferase activity);GO:0016740(transferase activity)
A_23_P167553	NM_000791	DHFR	NM_000791	Homo sapiens dihydrofolate reductase (DHFR), mRNA [NM_000791]	chr5	GO:0006545(glycine biosynthetic process);GO:0006730(one-carbon compound metabolic process);GO:0009165(nucleotide biosynthetic process)	GO:0005575(cellular_component)	GO:0004146(dihydrofolate reductase activity);GO:0016491(oxidoreductase activity);GO:0050661(NADP binding)
A_23_P15202	NM_001361	DHODH	NM_001361	Homo sapiens dihydroorotate dehydrogenase (DHODH), nuclear gene encoding mitochondrial protein, transcript variant 1, mRNA [NM_001361]	chr16	GO:0006207('de novo' pyrimidine base biosynthetic process);GO:0006221(pyrimidine nucleotide biosynthetic process);GO:0006222(UMP biosynthetic process);GO:0008152(metabolic process)	GO:0005739(mitochondrion);GO:0005743(mitochondrial inner membrane);GO:0016020(membrane)	GO:0003824(catalytic activity);GO:0004152(dihydroorotate dehydrogenase activity);GO:0004158(dihydroorotate oxidase activity);GO:0016491(oxidoreductase activity)
A_23_P321501	NM_182908	DHRS2	NM_182908	Homo sapiens dehydrogenase/reductase (SDR family) member 2 (DHRS2), transcript variant 1, mRNA [NM_182908]	chr14	GO:0006118(electron transport);GO:0008152(metabolic process);GO:0008207(C21-steroid hormone metabolic process);GO:0045786(negative regulation of progression through cell cycle)	GO:0005634(nucleus)	GO:0004022(alcohol dehydrogenase activity);GO:0016491(oxidoreductase activity)

A_32_P64919	NM_001042517	DIAPH3	NM_001042517	Homo sapiens diaphanous homolog 3 (Drosophila) (DIAPH3), transcript variant 1, mRNA [NM_001042517]	chr13	GO:0016043(cellular component organization and biogenesis);GO:0030036(actin cytoskeleton organization and biogenesis)		GO:0003779(actin binding);GO:0017048(Rho GTPase binding)
A_23_P127911	NM_015430	DKFZP586H2123	NM_015430	Homo sapiens regeneration associated muscle protease (DKFZP586H2123), transcript variant 1, mRNA [NM_015430]	chr11	GO:0006508(proteolysis)		GO:0004252(serine-type endopeptidase activity);GO:0008233(peptidase activity)
A_23_P24129	NM_012242	DKK1	NM_012242	Homo sapiens dickkopf homolog 1 (Xenopus laevis) (DKK1), mRNA [NM_012242]	chr10	GO:0007275(multicellular organismal development);GO:0016055(Wnt receptor signaling pathway);GO:0030178(negative regulation of Wnt receptor signaling pathway);GO:0030326(embryonic limb morphogenesis)	GO:0005576(extracellular region);GO:0005886(plasma membrane)	GO:0004871(signal transducer activity);GO:0005515(protein binding);GO:0008083(growth factor activity);GO:0050750(low-density lipoprotein receptor binding)
A_23_P88331	NM_014750	DLG7	NM_014750	Homo sapiens discs, large homolog 7 (Drosophila) (DLG7), mRNA [NM_014750]	chr14	GO:0000087(M phase of mitotic cell cycle);GO:0007049(cell cycle);GO:0007079(mitotic chromosome movement towards spindle pole);GO:0007267(cell-cell signaling);GO:0008283(cell proliferation);GO:0045842(positive regulation of mitotic metaphase/anaphase transition)	GO:0005634(nucleus)	GO:0004721(phosphoprotein phosphatase activity);GO:0005515(protein binding)
A_23_P361381	NM_007068	DMC1	NM_007068	Homo sapiens DMC1 dosage suppressor of mck1 homolog, meiosis-specific homologous recombination (yeast) (DMC1), mRNA [NM_007068]	chr22	GO:0001541(ovarian follicle development);GO:0006259(DNA metabolic process);GO:0007049(cell cycle);GO:0007126(meiosis);GO:0007131(meiotic recombination);GO:0007283(spermatogenesis);GO:0007292(female gamete generation)	GO:0000794(condensed nuclear chromosome);GO:0005622(intracellular);GO:0005634(nucleus)	GO:0000166(nucleotide binding);GO:0003677(DNA binding);GO:0005524(ATP binding);GO:0008094(DNA-dependent ATPase activity);GO:0017111(nucleoside-triphosphatase activity)
A_24_P288612	NM_007068	DMC1	NM_007068	Homo sapiens DMC1 dosage suppressor of mck1 homolog, meiosis-specific homologous recombination (yeast) (DMC1), mRNA [NM_007068]	chr22	GO:0001541(ovarian follicle development);GO:0006259(DNA metabolic process);GO:0007049(cell cycle);GO:0007126(meiosis);GO:0007131(meiotic recombination);GO:0007283(spermatogenesis);GO:0007292(female gamete generation)	GO:0000794(condensed nuclear chromosome);GO:0005622(intracellular);GO:0005634(nucleus)	GO:0000166(nucleotide binding);GO:0003677(DNA binding);GO:0005524(ATP binding);GO:0008094(DNA-dependent ATPase activity);GO:0017111(nucleoside-triphosphatase activity)
A_24_P366107	NM_001080449	DNA2L	NM_001080449	Homo sapiens DNA2 DNA replication helicase 2-like (yeast) (DNA2L), mRNA [NM_001080449]	chr10	GO:0006260(DNA replication)		GO:0000166(nucleotide binding);GO:0003677(DNA binding);GO:0004386(helicase activity);GO:0005524(ATP binding);GO:0016787(hydrolase activity)
A_23_P51339	NM_007034	DNAJB4	NM_007034	Homo sapiens DnaJ (Hsp40) homolog, subfamily B, member 4 (DNAJB4), mRNA [NM_007034]	chr1	GO:0006457(protein folding);GO:0006986(response to unfolded protein);GO:0009408(response to heat)		GO:0031072(heat shock protein binding);GO:0051082(unfolded protein binding)
A_23_P371266	NM_015569	DNM3	NM_015569	Homo sapiens dynamin 3 (DNM3), mRNA [NM_015569]	chr1	GO:0006412(translation);GO:0006897(endocytosis)	GO:0005622(intracellular);GO:0005840(ribosome);GO:0005874(microtubule)	GO:0000166(nucleotide binding);GO:0003735(structural constituent of ribosome);GO:0003774(motor activity);GO:0003924(GTPase activity);GO:0005515(protein binding);GO:0005525(GTP binding);GO:0016787(hydrolase activity)
A_23_P390528	NM_004420	DUSP8	NM_004420	Homo sapiens dual specificity phosphatase 8 (DUSP8), mRNA [NM_004420]	chr11	GO:0000188(inactivation of MAPK activity);GO:0006470(protein amino acid dephosphorylation)	GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0004725(protein tyrosine phosphatase activity);GO:0016787(hydrolase activity);GO:0017017(MAP kinase phosphatase activity)
A_24_P322867	NM_004420	DUSP8	NM_004420	Homo sapiens dual specificity phosphatase 8 (DUSP8), mRNA [NM_004420]	chr11	GO:0000188(inactivation of MAPK activity);GO:0006470(protein amino acid dephosphorylation)	GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0004725(protein tyrosine phosphatase activity);GO:0016787(hydrolase activity);GO:0017017(MAP kinase phosphatase activity)
A_23_P80032	NM_005225	E2F1	NM_005225	Homo sapiens E2F transcription factor 1 (E2F1), mRNA [NM_005225]	chr20	GO:0000074(regulation of progression through cell cycle);GO:0000080(G1 phase of mitotic cell cycle);GO:0000122(negative regulation of transcription from RNA polymerase II promoter);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006915(apoptosis);GO:0007049(cell cycle);GO:0008283(cell proliferation);GO:0030900(forebrain development);GO:0045944(positive regulation of transcription from RNA polymerase II promoter)	GO:0005634(nucleus);GO:0005667(transcription factor complex);GO:0005737(cytoplasm)	GO:0003700(transcription factor activity);GO:0003714(transcription corepressor activity);GO:0005515(protein binding);GO:0016563(transcriptional activator activity)
A_23_P408955	NM_004091	E2F2	NM_004091	Homo sapiens E2F transcription factor 2 (E2F2), mRNA [NM_004091]	chr1	GO:0000074(regulation of progression through cell cycle);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006367(transcription initiation from RNA polymerase II promoter);GO:0007049(cell cycle)	GO:0005634(nucleus);GO:0005667(transcription factor complex)	GO:0003700(transcription factor activity);GO:0003702(RNA polymerase II transcription factor activity);GO:0005515(protein binding)
A_23_P381645	NM_001005463	EBF3	NM_001005463	Homo sapiens early B-cell factor 3 (EBF3), mRNA [NM_001005463]	chr10	GO:0006355(regulation of transcription, DNA-dependent);GO:0007275(multicellular organismal development)	GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0008270(zinc ion binding);GO:0030528(transcription regulator activity);GO:0046872(metal ion binding)
A_24_P400457	ENST00000287899	ENST00000287899		CUB domain containing protein 2 [Source:RefSeq_peptide;Acc:NP_963840] [ENST00000287899]	chr1	GO:0006118(electron transport)		GO:0016491(oxidoreductase activity)
A_23_P361027	ENST00000326678	ENST00000326678		Homo sapiens cDNA FLJ39251 fis, clone OCBBF2008701. [AK096570]	chr8			
A_23_P51797	ENST00000343253	ENST00000343253		sarcoma antigen NY-SAR-41 [Source:RefSeq_peptide;Acc:NP_996769] [ENST00000343253]	chr1			
A_23_P80551	ENST00000383748	ENST00000383748		C3orf41 protein. [Source:Uniprot/SPTREMBL;Acc:Q0VFW9] [ENST00000383748]	chr3	GO:0006355(regulation of transcription, DNA-dependent)	GO:0005622(intracellular)	GO:0003676(nucleic acid binding)
A_23_P216556	NM_018424	EPB41L4B	NM_018424	Homo sapiens erythrocyte membrane protein band 4.1 like 4B (EPB41L4B), transcript variant 1, mRNA [NM_018424]	chr9		GO:0005737(cytoplasm);GO:0005856(cytoskeleton);GO:0016020(membrane)	GO:0005200(structural constituent of cytoskeleton);GO:0005488(binding);GO:0008092(cytoskeletal protein binding)

A_24_P11384	NM_018948	ERRFI1	NM_018948	Homo sapiens ERBB receptor feedback inhibitor 1 (ERRFI1), mRNA [NM_018948]	chr1	GO:0006950(response to stress)	GO:0005737(cytoplasm)	GO:0005100(Rho GTPase activator activity);GO:0005515(protein binding)
A_24_P323598	NM_001017420	ESCO2	NM_001017420	Homo sapiens establishment of cohesion 1 homolog 2 (S. cerevisiae) (ESCO2), mRNA [NM_001017420]	chr8	GO:0007049(cell cycle)	GO:0005634(nucleus)	GO:0008270(zinc ion binding);GO:0008415(acyltransferase activity);GO:0016740(transferase activity);GO:0046872(metal ion binding)
A_23_P32707	NM_012291	ESPL1	NM_012291	Homo sapiens extra spindle pole bodies homolog 1 (S. cerevisiae) (ESPL1), mRNA [NM_012291]	chr12	GO:0000070(mitotic sister chromatid segregation);GO:0000074(regulation of progression through cell cycle);GO:0000212(meiotic spindle organization and biogenesis);GO:0000910(cytokinesis);GO:0006508(proteolysis); GO:0006915(apoptosis);GO:0007059(chromosome segregation);GO:0040001(establishment of mitotic spindle localization);GO:0045143(homologous chromosome segregation);GO:0045842(positive regulation of mitotic metaphase/anaphase transition);GO:0045875(negative regulation of sister chromatid cohesion)	GO:0005634(nucleus);GO:0005813(centrosome)	GO:0005515(protein binding);GO:0008234(cysteine-type peptidase activity)
A_23_P23303	NM_003686	EXO1	NM_003686	Homo sapiens exonuclease 1 (EXO1), transcript variant 3, mRNA [NM_003686]	chr1	GO:0006281(DNA repair);GO:0006289(nucleotide-excision repair);GO:0006298(mismatch repair);GO:0006310(DNA recombination);GO:0006955(immune response);GO:0007126(meiosis)	GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0004519(endonuclease activity);GO:0004523(ribonuclease H activity);GO:0004527(exonuclease activity);GO:0005515(protein binding);GO:0016787(hydrolase activity);GO:0045145(single-stranded DNA specific 5'-3' exodeoxyribonuclease activity);GO:0048256(flap endonuclease activity)
A_24_P208703	NM_007177	FAM107A	NM_007177	Homo sapiens family with sequence similarity 107, member A (FAM107A), transcript variant 1, mRNA [NM_007177]	chr3	GO:0001558(regulation of cell growth)	GO:0005634(nucleus)	GO:0003674(molecular_function);GO:0005515(protein binding)
A_23_P203332	NM_022074	FAM111A	NM_022074	Homo sapiens family with sequence similarity 111, member A (FAM111A), transcript variant 1, mRNA [NM_022074]	chr11			
A_32_P12021	ENST00000368599	FAM26E		Uncharacterized protein C6orf188. [Source:Uniprot/SWISSPROT;Acc:Q8N5C1] [ENST00000368599]	chr6		GO:0016020(membrane);GO:0016021(integral to membrane)	
A_23_P253752	NM_138419	FAM54A	NM_138419	Homo sapiens family with sequence similarity 54, member A (FAM54A), mRNA [NM_138419]	chr6			
A_23_P49878	NM_019013	FAM64A	NM_019013	Homo sapiens family with sequence similarity 64, member A (FAM64A), mRNA [NM_019013]	chr17			
A_32_P151800	NM_207418	FAM72A	NM_207418	Homo sapiens family with sequence similarity 72, member A (FAM72A), mRNA [NM_207418]	chr1_random			
A_23_P51376	NM_024522	FAM77C	NM_024522	Homo sapiens family with sequence similarity 77, member C (FAM77C), mRNA [NM_024522]	chr1		GO:0016020(membrane);GO:0016021(integral to membrane)	
A_23_P206441	NM_000135	FANCA	NM_000135	Homo sapiens Fanconi anemia, complementation group A (FANCA), transcript variant 1, mRNA [NM_000135]	chr16	GO:0006281(DNA repair);GO:0006461(protein complex assembly)	GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0005515(protein binding)
A_23_P32021	NM_000136	FANCC	NM_000136	Homo sapiens Fanconi anemia, complementation group C (FANCC), mRNA [NM_000136]	chr9	GO:0006281(DNA repair);GO:0006289(nucleotide-excision repair);GO:0006461(protein complex assembly);GO:0007281(germ cell development)	GO:0005634(nucleus);GO:0005737(cytoplasm);GO:0005829(cytosol)	GO:0005515(protein binding)
A_32_P24165	NM_001018115	FANCD2	NM_001018115	Homo sapiens Fanconi anemia, complementation group D2 (FANCD2), transcript variant 2, mRNA [NM_001018115]	chr3	GO:0006281(DNA repair);GO:0007049(cell cycle);GO:0008150(biological_process)	GO:0000793(condensed chromosome);GO:0005575(cellular_component);GO:0005634(nucleus)	GO:0003674(molecular_function);GO:0005515(protein binding)
A_23_P71644	NM_004629	FANCG	NM_004629	Homo sapiens Fanconi anemia, complementation group G (FANCG), mRNA [NM_004629]	chr9	GO:0000075(cell cycle checkpoint);GO:0001541(ovarian follicle development);GO:0006281(DNA repair);GO:0007286(spermatid development);GO:0009314(response to radiation)	GO:0005634(nucleus)	GO:0003684(damaged DNA binding);GO:0005488(binding)
A_23_P375104	NM_018193	FANCI	NM_018193	Homo sapiens KIAA1794 (KIAA1794), mRNA [NM_018193]	chr15		GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005515(protein binding)
A_24_P902509	NM_018193	FANCI	NM_018193	Homo sapiens KIAA1794 (KIAA1794), mRNA [NM_018193]	chr15		GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005515(protein binding)
A_32_P95729	NM_018193	FANCI	NM_018193	Homo sapiens KIAA1794 (KIAA1794), mRNA [NM_018193]	chr15		GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005515(protein binding)
A_23_P218358	NM_031456	FBXW10	NM_031456	Homo sapiens F-box and WD repeat domain containing 10 (FBXW10), mRNA [NM_031456]	chr17			GO:0016874(ligase activity)

A_24_P73158	NM_004111	FEN1	NM_004111	Homo sapiens flap structure-specific endonuclease 1 (FEN1), mRNA [NM_004111]	chr11	GO:0006260(DNA replication);GO:0006302(double-strand break repair);GO:0009650(UV protection);GO:0048015(phosphoinositide-mediated signaling)	GO:0005634(nucleus)	GO:0000287(magnesium ion binding);GO:0003684(damaged DNA binding);GO:0003690(double-stranded DNA binding);GO:0004519(endonuclease activity);GO:0004523(ribonuclease H activity);GO:0005515(protein binding);GO:0008309(double-stranded DNA specific exodeoxyribonuclease activity);GO:0008409(5'-3' exonuclease activity);GO:0016787(hydrolase activity);GO:0017108(5'-flap endonuclease activity);GO:0030145(manganese ion binding)
A_24_P84898	NM_004111	FEN1	NM_004111	Homo sapiens flap structure-specific endonuclease 1 (FEN1), mRNA [NM_004111]	chr11	GO:0006260(DNA replication);GO:0006302(double-strand break repair);GO:0009650(UV protection);GO:0048015(phosphoinositide-mediated signaling)	GO:0005634(nucleus)	GO:0000287(magnesium ion binding);GO:0003684(damaged DNA binding);GO:0003690(double-stranded DNA binding);GO:0004519(endonuclease activity);GO:0004523(ribonuclease H activity);GO:0005515(protein binding);GO:0008309(double-stranded DNA specific exodeoxyribonuclease activity);GO:0008409(5'-3' exonuclease activity);GO:0016787(hydrolase activity);GO:0017108(5'-flap endonuclease activity);GO:0030145(manganese ion binding)
A_24_P158946	NM_139241	FGD4	NM_139241	Homo sapiens FYVE, RhoGEF and PH domain containing 4 (FGD4), mRNA [NM_139241]	chr12	GO:0007010(cytoskeleton organization and biogenesis);GO:0008360(regulation of cell shape);GO:0030036(actin cytoskeleton organization and biogenesis);GO:0035023(regulation of Rho protein signal transduction);GO:0043088(regulation of Cdc42 GTPase activity);GO:0046847(filopodium formation)	GO:0001726(ruffle);GO:0005622(intracellular);GO:0005737(cytoplasm);GO:0005794(Golgi apparatus);GO:0005856(cytoskeleton);GO:0030027(lamellipodium)	GO:0003779(actin binding);GO:0005085(guanyl-nucleotide exchange factor activity);GO:0005089(Rho guanyl-nucleotide exchange factor activity);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0031267(small GTPase binding);GO:0046872(metal ion binding)
A_24_P401855	NM_004464	FGF5	NM_004464	Homo sapiens fibroblast growth factor 5 (FGF5), transcript variant 1, mRNA [NM_004464]	chr4	GO:0000074(regulation of progression through cell cycle);GO:0007267(cell-cell signaling);GO:0007399(nervous system development);GO:0008283(cell proliferation);GO:0008543(fibroblast growth factor receptor signaling pathway)	GO:0005615(extracellular space)	GO:0008083(growth factor activity)
A_23_P42969	NM_006682	FGL2	NM_006682	Homo sapiens fibrinogen-like 2 (FGL2), mRNA [NM_006682]	chr7	GO:0007165(signal transduction)	GO:0005577(fibrinogen complex)	GO:0005102(receptor binding)
A_23_P302681	NM_022116	FIGNL1	NM_022116	Homo sapiens fidgetin-like 1 (FIGNL1), transcript variant 2, mRNA [NM_022116]	chr7			GO:0000166(nucleotide binding);GO:0005524(ATP binding);GO:0017111(nucleoside-triphosphatase activity)
A_24_P38081	NM_004117	FKBP5	NM_004117	Homo sapiens FK506 binding protein 5 (FKBP5), mRNA [NM_004117]	chr6	GO:0006457(protein folding)	GO:0005634(nucleus)	GO:0003755(peptidyl-prolyl cis-trans isomerase activity);GO:0005515(protein binding);GO:0005528(FK506 binding);GO:0016853(isomerase activity)
A_24_P230570	NM_004118	FKHL18	NM_004118	Homo sapiens forkhead-like 18 (Drosophila) (FKHL18), mRNA [NM_004118]	chr20	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0007275(multicellular organismal development);GO:0040018(positive regulation of body size);GO:0050885(regulation of balance)	GO:0005634(nucleus)	GO:0003700(transcription factor activity)
A_23_P96325	NM_001009954	FLJ20105	NM_001009954	Homo sapiens FLJ20105 protein (FLJ20105), transcript variant 2, mRNA [NM_001009954]	chrX			GO:0003677(DNA binding);GO:0004386(helicase activity);GO:0005515(protein binding);GO:0005524(ATP binding)
A_32_P197942	AK125261	FLJ23834	AK125261	Homo sapiens cDNA FLJ43271 fis, clone KIDNE2002882, highly similar to Homo sapiens Cadherin. [AK125261]	chr7	GO:0007156(homophilic cell adhesion)	GO:0016020(membrane)	GO:0005509(calcium ion binding)
A_23_P351837	NM_001039548	FLJ33790	NM_001039548	Homo sapiens hypothetical protein FLJ33790 (FLJ33790), mRNA [NM_001039548]	chr11			
A_23_P39574	NM_001080539	FLJ39660	NM_001080539	Homo sapiens hypothetical protein FLJ39660 (FLJ39660), mRNA [NM_001080539]	chr2			
A_24_P177585	NM_182625	FLJ40869	NM_182625	Homo sapiens hypothetical protein FLJ40869 (FLJ40869), mRNA [NM_182625]	chr2	GO:0006281(DNA repair)		GO:0004518(nuclease activity)
A_23_P151150	NM_202002	FOXM1	NM_202002	Homo sapiens forkhead box M1 (FOXM1), transcript variant 1, mRNA [NM_202002]	chr12	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent)	GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0005515(protein binding)
A_24_P379165	NM_005938	FOXO4	NM_005938	Homo sapiens myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 7 (MLLT7), mRNA [NM_005938]	chrX	GO:0000080(G1 phase of mitotic cell cycle);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006366(transcription from RNA polymerase II promoter);GO:0007049(cell cycle);GO:0007050(cell cycle arrest);GO:0007275(multicellular organismal development);GO:0007519(striated muscle development);GO:0008285(negative regulation of cell proliferation);GO:0008286(insulin receptor signaling pathway);GO:0016525(negative regulation of angiogenesis);GO:0030154(cell differentiation);GO:0051151(negative regulation of smooth muscle cell differentiation)	GO:0005634(nucleus);GO:0005829(cytosol)	GO:0003700(transcription factor activity);GO:0008134(transcription factor binding);GO:0019899(enzyme binding)
A_23_P74609	NM_015714	G0S2	NM_015714	Homo sapiens G0/G1switch 2 (G0S2), mRNA [NM_015714]	chr1	GO:0000074(regulation of progression through cell cycle);GO:0007049(cell cycle)	GO:0005575(cellular_component)	GO:0003674(molecular_function)

A_23_P103996	NM_002061	GCLM	NM_002061	Homo sapiens glutamate-cysteine ligase, modifier subunit (GCLM), mRNA [NM_002061]	chr1	GO:0006534(cysteine metabolic process);GO:0006536(glutamate metabolic process);GO:0006750(glutathione biosynthetic process);GO:0006979(response to oxidative stress);GO:0035229(positive regulation of glutamate-cysteine ligase activity);GO:0042493(response to drug);GO:0050880(regulation of blood vessel size)	GO:0005625(soluble fraction);GO:0005829(cytosol);GO:0017109(glutamate-cysteine ligase complex)	GO:0004357(glutamate-cysteine ligase activity);GO:0005515(protein binding);GO:0016491(oxidoreductase activity);GO:0016874(ligase activity);GO:0035226(glutamate-cysteine ligase catalytic subunit binding);GO:0046982(protein heterodimerization activity)
A_32_P177953	ENST00000370238	GCLM		Glutamate--cysteine ligase regulatory subunit (EC 6.3.2.2) (Gamma-glutamylcysteine synthetase) (Gamma-ECS) (GCS light chain) (Glutamate--cysteine ligase modifier subunit). [Source:Uniprot/SWISSPROT;Acc:P48507] [ENST00000370238]	chr1	GO:0006534(cysteine metabolic process);GO:0006536(glutamate metabolic process);GO:0006749(glutathione metabolic process);GO:0006750(glutathione biosynthetic process);GO:0006979(response to oxidative stress);GO:0035229(positive regulation of glutamate-cysteine ligase activity);GO:0042493(response to drug);GO:0050880(regulation of blood vessel size)	GO:0005625(soluble fraction);GO:0005829(cytosol);GO:0017109(glutamate-cysteine ligase complex)	GO:0004357(glutamate-cysteine ligase activity);GO:0005515(protein binding);GO:0016491(oxidoreductase activity);GO:0016874(ligase activity);GO:0035226(glutamate-cysteine ligase catalytic subunit binding);GO:0046982(protein heterodimerization activity)
A_23_P9232	NM_001490	GCNT1	NM_001490	Homo sapiens glucosaminyl (N-acetyl) transferase 1, core 2 (beta-1,6-N-acetylglucosaminyltransferase) (GCNT1), mRNA [NM_001490]	chr9	GO:0006493(protein amino acid O-linked glycosylation)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0003829(beta-1,3-galactosyl-O-glycosyl-glycoprotein beta-1,6-N-acetylglucosaminyltransferase activity);GO:0016757(transferase activity, transferring glycosyl groups)
A_23_P136787	NM_032336	GINS4	NM_032336	Homo sapiens GINS complex subunit 4 (Sld5 homolog) (GINS4), mRNA [NM_032336]	chr8			
A_23_P39766	NM_014905	GLS	NM_014905	Homo sapiens glutaminase (GLS), mRNA [NM_014905]	chr2	GO:0006543(glutamine catabolic process)	GO:0005739(mitochondrion)	GO:0004359(glutaminase activity);GO:0016787(hydrolase activity)
A_24_P294233	NM_014905	GLS	NM_014905	Homo sapiens glutaminase (GLS), mRNA [NM_014905]	chr2	GO:0006543(glutamine catabolic process)	GO:0005739(mitochondrion)	GO:0004359(glutaminase activity);GO:0016787(hydrolase activity)
A_23_P99285	NM_006143	GPR19	NM_006143	Homo sapiens G protein-coupled receptor 19 (GPR19), mRNA [NM_006143]	chr12	GO:0007165(signal transduction);GO:0007186(G-protein coupled receptor protein signaling pathway)	GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0001584(rhodopsin-like receptor activity);GO:0004872(receptor activity)
A_23_P36825	NM_003979	GPRC5A	NM_003979	Homo sapiens G protein-coupled receptor, family C, group 5, member A (GPRC5A), mRNA [NM_003979]	chr12	GO:0007165(signal transduction);GO:0007186(G-protein coupled receptor protein signaling pathway)	GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0004872(receptor activity);GO:0008067(metabotropic glutamate, GABA-B-like receptor activity)
A_23_P63402	NM_013296	GPSM2	NM_013296	Homo sapiens G-protein signalling modulator 2 (AGS3-like, C. elegans) (GPSM2), mRNA [NM_013296]	chr1	GO:0007165(signal transduction);GO:0007186(G-protein coupled receptor protein signaling pathway)		GO:0005096(GTPase activator activity);GO:0005488(binding);GO:0042802(identical protein binding)
A_24_P273132	NM_013296	GPSM2	NM_013296	Homo sapiens G-protein signalling modulator 2 (AGS3-like, C. elegans) (GPSM2), mRNA [NM_013296]	chr1	GO:0007165(signal transduction);GO:0007186(G-protein coupled receptor protein signaling pathway)		GO:0005096(GTPase activator activity);GO:0005488(binding);GO:0042802(identical protein binding)
A_24_P76521	AK056691	GSG2	AK056691	Homo sapiens cDNA FLJ32129 fis, clone PEBLM2000213, weakly similar to Mus musculus genes for integrin aM290, hapsin. [AK056691]	chr17	GO:0000074(regulation of progression through cell cycle);GO:0006468(protein amino acid phosphorylation);GO:0007049(cell cycle);GO:0007243(protein kinase cascade);GO:0016568(chromatin modification)	GO:0005634(nucleus)	GO:0000166(nucleotide binding);GO:0000287(magnesium ion binding);GO:0004674(protein serine/threonine kinase activity);GO:0004713(protein-tyrosine kinase activity);GO:0005524(ATP binding);GO:0016740(transferase activity)
A_23_P26916	NM_001015053	HDAC5	NM_001015053	Homo sapiens histone deacetylase 5 (HDAC5), transcript variant 3, mRNA [NM_001015053]	chr17	GO:0000074(regulation of progression through cell cycle);GO:0006338(chromatin remodeling);GO:0006342(chromatin **silencing);GO:0006350(transcription);GO:0006355(regulation of** transcription, DNA-dependent);GO:0006954(inflammatory response);GO:0030183(B cell differentiation);GO:0045843(negative regulation of striated muscle development)	GO:0000118(histone deacetylase complex);GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0004407(histone deacetylase activity);GO:0008134(transcription factor binding);GO:0016566(specific transcriptional repressor **activity);GO:0016787(hydrolase activity)**
A_23_P26922	NM_001015053	HDAC5	NM_001015053	Homo sapiens histone deacetylase 5 (HDAC5), transcript variant 3, mRNA [NM_001015053]	chr17	GO:0000074(regulation of progression through cell cycle);GO:0006338(chromatin remodeling);GO:0006342(chromatin silencing);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006954(inflammatory response);GO:0030183(B cell differentiation);GO:0045843(negative regulation of striated muscle development)	GO:0000118(histone deacetylase complex);GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0004407(histone deacetylase activity);GO:0008134(transcription factor binding);GO:0016566(specific transcriptional repressor activity);GO:0016787(hydrolase activity)
A_23_P110196	NM_016323	HERC5	NM_016323	Homo sapiens hect domain and RLD 5 (HERC5), mRNA [NM_016323]	chr4	GO:0000079(regulation of cyclin-dependent protein kinase activity);GO:0006464(protein modification process);GO:0006512(ubiquitin cycle)	GO:0005622(intracellular)	GO:0004842(ubiquitin-protein ligase activity);GO:0016874(ligase activity)
A_24_P401842	AK074711	HHIP	AK074711	Homo sapiens cDNA FLJ90230 fis, clone NT2RM2000410. [AK074711]	chr4	GO:0007165(signal transduction);GO:0007224(smoothened signaling pathway);GO:0007405(neuroblast proliferation);GO:0009887(organ morphogenesis);GO:0009953(dorsal/ventral pattern formation);GO:0030324(lung development);GO:0040036(regulation of fibroblast growth factor receptor signaling pathway);GO:0045879(negative regulation of smoothened signaling pathway)	GO:0005887(integral to plasma membrane);GO:0009986(cell surface)	GO:0005515(protein binding)
A_24_P142269	NM_003609	HIRIP3	NM_003609	Homo sapiens HIRA interacting protein 3 (HIRIP3), mRNA [NM_003609]	chr16	GO:0006333(chromatin assembly or disassembly)	GO:0005634(nucleus)	
A_23_P309381	NM_003516	HIST2H2AA3	NM_003516	Homo sapiens histone cluster 2, H2aa3 (HIST2H2AA3), mRNA [NM_003516]	chr1	GO:0006334(nucleosome assembly);GO:0007001(chromosome organization and biogenesis (sensu Eukaryota))	GO:0000786(nucleosome);GO:0005634(nucleus);GO:00056 94(chromosome)	GO:0003677(DNA binding)

A_23_P398460	NM_000189	HK2	NM_000189	Homo sapiens hexokinase 2 (HK2), mRNA [NM_000189]	chr2	GO:0000074(regulation of progression through cell cycle);GO:0006096(glycolysis);GO:0046835(carbohydrate phosphorylation)	GO:0005741(mitochondrial outer membrane);GO:0016020(membrane)	GO:0000166(nucleotide binding);GO:0004396(hexokinase activity);GO:0005524(ATP binding);GO:0016301(kinase activity);GO:0016740(transferase activity)
A_32_P175739	NM_000189	HK2	NM_000189	Homo sapiens hexokinase 2 (HK2), mRNA [NM_000189]	chr2	GO:0000074(regulation of progression through cell cycle);GO:0006096(glycolysis);GO:0046835(carbohydrate phosphorylation)	GO:0005741(mitochondrial outer membrane);GO:0016020(membrane)	GO:0000166(nucleotide binding);GO:0004396(hexokinase activity);GO:0005524(ATP binding);GO:0016301(kinase activity);GO:0016740(transferase activity)
A_23_P202427	NM_025130	HKDC1	NM_025130	Homo sapiens hexokinase domain containing 1 (HKDC1), mRNA [NM_025130]	chr10	GO:0006096(glycolysis)		GO:0000166(nucleotide binding);GO:0004396(hexokinase activity);GO:0005524(ATP binding);GO:0016301(kinase activity);GO:0016740(transferase activity)
A_23_P120883	NM_002133	HMOX1	NM_002133	Homo sapiens heme oxygenase (decycling) 1 (HMOX1), mRNA [NM_002133]	chr22	GO:0006788(heme oxidation);GO:0043123(positive regulation of I-kappaB kinase/NF-kappaB cascade)	GO:0005624(membrane fraction);GO:0005783(endoplasmic reticulum);GO:0005792(microsome)	GO:0004392(heme oxygenase (decyclizing) activity);GO:0004871(signal transducer activity);GO:0005506(iron ion binding);GO:0016491(oxidoreductase activity);GO:0046872(metal ion binding)
A_23_P74449	NM_032756	HPDL	NM_032756	Homo sapiens 4-hydroxyphenylpyruvate dioxygenase-like (HPDL), mRNA [NM_032756]	chr1	GO:0009072(aromatic amino acid family metabolic process)		GO:0003868(4-hydroxyphenylpyruvate dioxygenase activity)
A_23_P363936	NM_014278	HSPA4L	NM_014278	Homo sapiens heat shock 70kDa protein 4-like (HSPA4L), mRNA [NM_014278]	chr4	GO:0006457(protein folding);GO:0006986(response to unfolded protein)	GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0000166(nucleotide binding);GO:0005515(protein binding);GO:0005524(ATP binding)
A_23_P127522	NM_145014	HYLS1	NM_145014	Homo sapiens hydrolethalus syndrome 1 (HYLS1), mRNA [NM_145014]	chr11		GO:0005634(nucleus);GO:0005737(cytoplasm)	
A_23_P42868	NM_000596	IGFBP1	NM_000596	Homo sapiens insulin-like growth factor binding protein 1 (IGFBP1), transcript variant 1, mRNA [NM_000596]	chr7	GO:0001558(regulation of cell growth);GO:0007165(signal transduction)	GO:0005576(extracellular region);GO:0005615(extracellular space)	GO:0005520(insulin-like growth factor binding)
A_23_P67169	NM_000641	IL11	NM_000641	Homo sapiens interleukin 11 (IL11), mRNA [NM_000641]	chr19	GO:0007267(cell-cell signaling);GO:0008284(positive regulation of cell proliferation);GO:0030168(platelet activation);GO:0030183(B cell differentiation);GO:0030219(megakaryocyte differentiation);GO:0045444(fat cell differentiation)	GO:0005576(extracellular region);GO:0005615(extracellular space)	GO:0005125(cytokine activity);GO:0005142(interleukin-11 receptor binding)
A_24_P227927	NM_181078	IL21R	NM_181078	Homo sapiens interleukin 21 receptor (IL21R), transcript variant 2, mRNA [NM_181078]	chr16	GO:0030101(natural killer cell activation)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0001532(interleukin-21 receptor activity);GO:0004872(receptor activity)
A_23_P381992	NM_002210	ITGAV	NM_002210	Homo sapiens integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51) (ITGAV), mRNA [NM_002210]	chr2	GO:0007155(cell adhesion);GO:0007160(cell-matrix adhesion);GO:0007229(integrin-mediated signaling pathway)	GO:0008305(integrin complex);GO:0016020(membrane)	GO:0004872(receptor activity);GO:0005509(calcium ion binding);GO:0005515(protein binding)
A_23_P50907	NM_002210	ITGAV	NM_002210	Homo sapiens integrin, alpha V (vitronectin receptor, alpha polypeptide, antigen CD51) (ITGAV), mRNA [NM_002210]	chr2	GO:0007155(cell adhesion);GO:0007160(cell-matrix adhesion);GO:0007229(integrin-mediated signaling pathway)	GO:0008305(integrin complex);GO:0016020(membrane)	GO:0004872(receptor activity);GO:0005509(calcium ion binding);GO:0005515(protein binding)
A_23_P23765	NM_014288	ITGB3BP	NM_014288	Homo sapiens integrin beta 3 binding protein (beta3-endonexin) (ITGB3BP), mRNA [NM_014288]	chr1	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006915(apoptosis);GO:0007155(cell adhesion);GO:0007165(signal transduction)	GO:0000775(chromosome, pericentric region);GO:0005624(membrane fraction);GO:0005634(nucleus);GO:0005694(chromosome);GO:0005737(cytoplasm)	GO:0004871(signal transducer activity);GO:0008022(protein C-terminus binding)
A_23_P334630	NM_003724	JRK	NM_003724	Homo sapiens jerky homolog (mouse) (JRK), transcript variant 1, mRNA [NM_003724]	chr8	GO:0008150(biological_process);GO:0045449(regulation of transcription)	GO:0000775(chromosome, pericentric region);GO:0005575(cellular_component);GO:0005634(nucleus)	GO:0003674(molecular_function);GO:0003677(DNA binding)
A_24_P339429	NM_021012	KCNJ12	NM_021012	Homo sapiens potassium inwardly-rectifying channel, subfamily J, member 12 (KCNJ12), mRNA [NM_021012]	chr17	GO:0006811(ion transport);GO:0006813(potassium ion transport);GO:0006936(muscle contraction);GO:0008015(circulation);GO:0008016(regulation of heart contraction)	GO:0005624(membrane fraction);GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0005242(inward rectifier potassium channel activity);GO:0005244(voltage-gated ion channel activity);GO:0030955(potassium ion binding)
A_23_P329261	NM_000891	KCNJ2	NM_000891	Homo sapiens potassium inwardly-rectifying channel, subfamily J, member 2 (KCNJ2), mRNA [NM_000891]	chr17	GO:0006811(ion transport);GO:0006813(potassium ion transport)	GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0005242(inward rectifier potassium channel activity);GO:0005244(voltage-gated ion channel activity);GO:0005515(protein binding);GO:0030955(potassium ion binding)
A_23_P5845	NM_000221	KHK	NM_000221	Homo sapiens ketohexokinase (fructokinase) (KHK), transcript variant a, mRNA [NM_000221]	chr2	GO:0005975(carbohydrate metabolic process)	GO:0005737(cytoplasm)	GO:0004454(ketohexokinase activity);GO:0005515(protein binding);GO:0016301(kinase activity);GO:0016740(transferase activity)
A_23_P53346	NM_015257	KIAA0286	NM_015257	Homo sapiens KIAA0286 protein (KIAA0286), mRNA [NM_015257]	chr12	GO:0008150(biological_process)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0003674(molecular_function)
A_24_P126628	NM_015257	KIAA0286	NM_015257	Homo sapiens KIAA0286 protein (KIAA0286), mRNA [NM_015257]	chr12	GO:0008150(biological_process)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0003674(molecular_function)
A_23_P426021	NM_015187	KIAA0746	NM_015187	Homo sapiens KIAA0746 protein (KIAA0746), mRNA [NM_015187]	chr4			GO:0005488(binding)
A_23_P358714	AY358366	KIAA1324	AY358366	Homo sapiens clone DNA59770 AEPG2426 (UNQ2426) mRNA, complete cds. [AY358366]	chr1			
A_23_P99604	NM_017769	KIAA1333	NM_017769	Homo sapiens KIAA1333 (KIAA1333), mRNA [NM_017769]	chr14	GO:0006464(protein modification process);GO:0006512(ubiquitin cycle)	GO:0005622(intracellular)	GO:0004842(ubiquitin-protein ligase activity);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0016874(ligase activity);GO:0046872(metal ion binding)

A_23_P52278	NM_004523	KIF11	NM_004523	Homo sapiens kinesin family member 11 (KIF11), mRNA [NM_004523]	chr10	GO:0007018(microtubule-based movement);GO:0007049(cell cycle);GO:0007052(mitotic spindle organization and biogenesis);GO:0007067(mitosis);GO:0007100(mitotic centrosome separation);GO:0051300(spindle pole body organization and biogenesis);GO:0051301(cell division)	GO:0000922(spindle pole);GO:0005871(kinesin complex);GO:0005876(spindle microtubule)	GO:0000166(nucleotide binding);GO:0003777(microtubule motor activity);GO:0005524(ATP binding)
A_23_P80902	NM_020242	KIF15	NM_020242	Homo sapiens kinesin family member 15 (KIF15), mRNA [NM_020242]	chr3	GO:0007018(microtubule-based movement);GO:0007067(mitosis);GO:0008283(cell proliferation)	GO:0005813(centrosome);GO:0005873(plus-end kinesin complex);GO:0005874(microtubule);GO:0005875(microtubule associated complex)	GO:0000166(nucleotide binding);GO:0003677(DNA binding);GO:0003777(microtubule motor activity);GO:0004872(receptor activity);GO:0005524(ATP binding)
A_23_P34788	NM_006845	KIF2C	NM_006845	Homo sapiens kinesin family member 2C (KIF2C), mRNA [NM_006845]	chr1	GO:0007018(microtubule-based movement);GO:0007067(mitosis);GO:0008283(cell proliferation);GO:0030951(establishment and/or maintenance of microtubule cytoskeleton polarity)	GO:0000775(chromosome, pericentric region);GO:0005634(nucleus);GO:0005871(kinesin complex);GO:0005874(microtubule)	GO:0000166(nucleotide binding);GO:0003777(microtubule motor activity);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0019237(centromeric DNA binding)
A_24_P20327	NM_014079	KLF15	NM_014079	Homo sapiens Kruppel-like factor 15 (KLF15), mRNA [NM_014079]	chr3	GO:0006350(transcription);GO:0015758(glucose transport);GO:0045893(positive regulation of transcription, DNA-dependent)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_24_P521994	NM_017644	KLHL24	NM_017644	Homo sapiens kelch-like 24 (Drosophila) (KLHL24), mRNA [NM_017644]	chr3			GO:0005515(protein binding)
A_23_P125265	NM_002266	KPNA2	NM_002266	Homo sapiens karyopherin alpha 2 (RAG cohort 1, importin alpha 1) (KPNA2), mRNA [NM_002266]	chr17	GO:0000018(regulation of DNA recombination);GO:0000072(M phase specific microtubule process);GO:0000085(G2 phase of mitotic cell cycle);GO:0006259(DNA metabolic process);GO:0006606(protein import into nucleus);GO:0006607(NLS-bearing substrate import into nucleus);GO:0006886(intracellular protein transport)	GO:0005634(nucleus);GO:0005643(nuclear pore);GO:0005654(nucleoplasm);GO:0005737(cytoplasm)	GO:0005488(binding);GO:0005515(protein binding);GO:0008139(nuclear localization sequence binding);GO:0008565(protein transporter activity)
A_23_P91697	NM_004737	LARGE	NM_004737	Homo sapiens like-glycosyltransferase (LARGE), transcript variant 1, mRNA [NM_004737]	chr22	GO:0006044(N-acetylglucosamine metabolic process);GO:0006486(protein amino acid glycosylation);GO:0006688(glycosphingolipid biosynthetic process);GO:0016051(carbohydrate biosynthetic process);GO:0046716(muscle maintenance)	GO:0016020(membrane);GO:0016021(integral to membrane);GO:0030173(integral to Golgi membrane)	GO:0008375(acetylglucosaminyltransferase activity)
A_23_P120227	NM_030915	LBH	NM_030915	Homo sapiens limb bud and heart development homolog (mouse) (LBH), mRNA [NM_030915]	chr2			
A_24_P182858	NM_030915	LBH	NM_030915	Homo sapiens limb bud and heart development homolog (mouse) (LBH), mRNA [NM_030915]	chr2			
A_23_P6771	NM_014583	LMCD1	NM_014583	Homo sapiens LIM and cysteine-rich domains 1 (LMCD1), mRNA [NM_014583]	chr3	GO:0000122(negative regulation of transcription from RNA polymerase II promoter);GO:0008150(biological_process)	GO:0005575(cellular_component);GO:0005634(nucleus)	GO:0003674(molecular_function);GO:0003714(transcription corepressor activity);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_24_P680947	ENST00000335534	LOC146909		Homo sapiens hypothetical protein LOC146909, mRNA (cDNA clone IMAGE:4418755), partial cds. [BC048263]	chr17	GO:0007018(microtubule-based movement)	GO:0005875(microtubule associated complex)	GO:0003777(microtubule motor activity);GO:0005524(ATP binding)
A_23_P41476	NM_001080505	LOC152573	NM_001080505	Homo sapiens hypothetical protein BC012029 (LOC152573), mRNA [NM_001080505]	chr4			
A_32_P192922	AL050061	LOC157562	AL050061	Homo sapiens mRNA; cDNA DKFZp566J123 (from clone DKFZp566J123). [AL050061]	chr8			
A_24_P734060	AL832183	LOC284454	AL832183	Homo sapiens mRNA; cDNA DKFZp686D0720 (from clone DKFZp686D0720). [AL832183]	chr19			
A_24_P195400	XR_019065	LOC391247	XR_019065	PREDICTED: Homo sapiens similar to DNA replication complex GINS protein PSF2 (LOC391247), mRNA [XR_019065]	chr20			
A_24_P127462	XR_018314	LOC392454	XR_018314	PREDICTED: Homo sapiens similar to Proliferating cell nuclear antigen (PCNA) (Cyclin) (LOC392454), mRNA [XR_018314]	chrX			
A_24_P67494	XR_019062	LOC643513	XR_019062	PREDICTED: Homo sapiens similar to Importin alpha-2 subunit (Karyopherin alpha-2 subunit) (SRP1-alpha) (RAG cohort protein 1) (LOC643513), mRNA [XR_019062]	chr4			
A_24_P565908	XR_017068	LOC646091	XR_017068	PREDICTED: Homo sapiens similar to Replication factor C subunit 2 (Replication factor C 40 kDa subunit) (RF-C 40 kDa subunit) (RFC40) (Activator 1 40 kDa subunit) (A1 40 kDa subunit) (LOC646091), mRNA [XR_017068]	chr2			
A_32_P16625	XM_001130587	LOC728688	XM_001130587	PREDICTED: Homo sapiens hypothetical protein LOC728688 (LOC728688), mRNA [XM_001130587]	chr12			
A_24_P804667	NM_001043229	LOC751071	NM_001043229	Homo sapiens hypothetical protein LOC751071 (LOC751071), mRNA [NM_001043229]	chr11	GO:0008152(metabolic process)		GO:0008168(methyltransferase activity)

A_23_P49459	NM_030941	LOC81691	NM_030941	Homo sapiens exonuclease NEF-sp (LOC81691), mRNA [NM_030941]	chr16		GO:0005622(intracellular);GO:0005730(nucleolus)	GO:0000166(nucleotide binding);GO:0003676(nucleic acid binding);GO:0004527(exonuclease activity)
A_23_P213166	NM_138698	LOC91431	NM_138698	Homo sapiens prematurely terminated mRNA decay factor-like (LOC91431), mRNA [NM_138698]	chr4			GO:0008270(zinc ion binding)
A_23_P426511	NM_138698	LOC91431	NM_138698	Homo sapiens prematurely terminated mRNA decay factor-like (LOC91431), mRNA [NM_138698]	chr4			GO:0008270(zinc ion binding)
A_23_P47885	NM_153377	LRIG3	NM_153377	Homo sapiens leucine-rich repeats and immunoglobulin-like domains 3 (LRIG3), mRNA [NM_153377]	chr12		GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005515(protein binding)
A_23_P6674	NM_020169	LXN	NM_020169	Homo sapiens latexin (LXN), mRNA [NM_020169]	chr3	GO:0050965(detection of temperature stimulus during sensory perception of pain)		GO:0004857(enzyme inhibitor activity);GO:0005515(protein binding);GO:0008191(metalloendopeptidase inhibitor activity)
A_24_P37253	NM_194317	LYPD6	NM_194317	Homo sapiens LY6/PLAUR domain containing 6 (LYPD6), mRNA [NM_194317]	chr2			
A_23_P78209	NM_002359	MAFG	NM_002359	Homo sapiens v-maf musculoaponeurotic fibrosarcoma oncogene homolog G (avian) (MAFG), transcript variant 1, mRNA [NM_002359]	chr17	GO:0001701(in utero embryonic development);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006366(transcription from RNA polymerase II promoter);GO:0030534(adult behavior);GO:0042127(regulation of cell proliferation);GO:0045604(regulation of epidermal cell differentiation)	GO:0000785(chromatin);GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0046983(protein dimerization activity)
A_23_P161474	NM_182751	MCM10	NM_182751	Homo sapiens MCM10 minichromosome maintenance deficient 10 (S. cerevisiae) (MCM10), transcript variant 1, mRNA [NM_182751]	chr10	GO:0000074(regulation of progression through cell cycle);GO:0006260(DNA replication)	GO:0005634(nucleus)	GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_24_P412088	NM_182751	MCM10	NM_182751	Homo sapiens MCM10 minichromosome maintenance deficient 10 (S. cerevisiae) (MCM10), transcript variant 1, mRNA [NM_182751]	chr10	GO:0000074(regulation of progression through cell cycle);GO:0006260(DNA replication)	GO:0005634(nucleus)	GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_32_P103633	NM_004526	MCM2	NM_004526	Homo sapiens MCM2 minichromosome maintenance deficient 2, mitotin (S. cerevisiae) (MCM2), mRNA [NM_004526]	chr3	GO:0006260(DNA replication);GO:0006268(DNA unwinding during replication);GO:0006270(DNA replication initiation);GO:0006334(nucleosome assembly);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0007049(cell cycle)	GO:0000785(chromatin);GO:0005634(nucleus);GO:0005664(nuclear origin of replication recognition complex)	GO:0000166(nucleotide binding);GO:0003677(DNA binding);GO:0003688(DNA replication origin binding);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0008094(DNA-dependent ATPase activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P68547	NM_182802	MCM8	NM_182802	Homo sapiens MCM8 minichromosome maintenance deficient 8 (S. cerevisiae) (MCM8), transcript variant 2, mRNA [NM_182802]	chr20	GO:0006260(DNA replication);GO:0006270(DNA replication initiation);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0007049(cell cycle)	GO:0005634(nucleus)	GO:0000166(nucleotide binding);GO:0003677(DNA binding);GO:0005524(ATP binding);GO:0008094(DNA-dependent ATPase activity);GO:0017111(nucleoside-triphosphatase activity)
A_24_P305556	NM_182802	MCM8	NM_182802	Homo sapiens MCM8 minichromosome maintenance deficient 8 (S. cerevisiae) (MCM8), transcript variant 2, mRNA [NM_182802]	chr20	GO:0006260(DNA replication);GO:0006270(DNA replication initiation);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0007049(cell cycle)	GO:0005634(nucleus)	GO:0000166(nucleotide binding);GO:0003677(DNA binding);GO:0005524(ATP binding);GO:0008094(DNA-dependent ATPase activity);GO:0017111(nucleoside-triphosphatase activity)
A_24_P314640	NM_153487	MDGA1	NM_153487	Homo sapiens MAM domain containing glycosylphosphatidylinositol anchor 1 (MDGA1), mRNA [NM_153487]	chr6		GO:0016020(membrane)	
A_23_P422026	NM_002395	ME1	NM_002395	Homo sapiens malic enzyme 1, NADP(+)-dependent, cytosolic (ME1), mRNA [NM_002395]	chr6	GO:0005975(carbohydrate metabolic process);GO:0006108(malate metabolic process);GO:0006741(NADP biosynthetic process);GO:0009725(response to hormone stimulus);GO:0009743(response to carbohydrate stimulus)	GO:0005829(cytosol)	GO:0004473(malate dehydrogenase (oxaloacetate-decarboxylating) (NADP+) activity);GO:0009055(electron carrier activity);GO:0030145(manganese ion binding);GO:0046872(metal ion binding);GO:0050661(NADP binding);GO:0051287(NAD binding)
A_24_P1731	NM_005587	MEF2A	NM_005587	Homo sapiens MADS box transcription enhancer factor 2, polypeptide A (myocyte enhancer factor 2A) (MEF2A), mRNA [NM_005587]	chr15	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006366(transcription from RNA polymerase II promoter);GO:0007517(muscle development)	GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0003713(transcription coactivator activity)
A_23_P156970	NM_002402	MEST	NM_002402	Homo sapiens mesoderm specific transcript homolog (mouse) (MEST), transcript variant 1, mRNA [NM_002402]	chr7		GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0003824(catalytic activity)
A_23_P415021	NM_014033	METTL7A	NM_014033	Homo sapiens methyltransferase like 7A (METTL7A), mRNA [NM_014033]	chr12	GO:0008152(metabolic process)		GO:0008168(methyltransferase activity);GO:0016740(transferase activity)
A_23_P406227	AY203928	MGC23284	AY203928	Homo sapiens FP17581 mRNA, complete cds. [AY203928]	chr16			
A_23_P254733	NM_024629	MLF1IP	NM_024629	Homo sapiens MLF1 interacting protein (MLF1IP), mRNA [NM_024629]	chr4	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent)	GO:0000775(chromosome, pericentric region);GO:0005634(nucleus);GO:0005694(chromosome)	
A_24_P83586	NM_015506	MMACHC	NM_015506	Homo sapiens methylmalonic aciduria (cobalamin deficiency) cblC type, with homocystinuria (MMACHC), mRNA [NM_015506]	chr1			GO:0031419(cobalamin binding);GO:0050897(cobalt ion binding)

A_23_P133123	NM_032117	MND1	NM_032117	Homo sapiens meiotic nuclear divisions 1 homolog (S. cerevisiae) (MND1), mRNA [NM_032117]	chr4			
A_23_P3302	NM_018365	MNS1	NM_018365	Homo sapiens meiosis-specific nuclear structural 1 (MNS1), mRNA [NM_018365]	chr15			
A_23_P110430	NM_002448	MSX1	NM_002448	Homo sapiens msh homeobox 1 (MSX1), mRNA [NM_002448]	chr4	GO:0000122(negative regulation of transcription from RNA polymerase II promoter);GO:0001501(skeletal development);GO:0007275(multicellular organismal development);GO:0007517(muscle development);GO:0009887(organ morphogenesis);GO:0030326(embryonic limb morphogenesis);GO:0030900(forebrain development);GO:0030901(midbrain development)	GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0005515(protein binding);GO:0016564(transcriptional repressor activity)
A_24_P345837	NM_002448	MSX1	NM_002448	Homo sapiens msh homeobox 1 (MSX1), mRNA [NM_002448]	chr4	GO:0000122(negative regulation of transcription from RNA polymerase II promoter);GO:0001501(skeletal development);GO:0007275(multicellular organismal development);GO:0007517(muscle development);GO:0009887(organ morphogenesis);GO:0030326(embryonic limb morphogenesis);GO:0030900(forebrain development);GO:0030901(midbrain development)	GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0005515(protein binding);GO:0016564(transcriptional repressor activity)
A_24_P110770	AK074050	MYO1G	AK074050	Homo sapiens mRNA for FLJ00121 protein. [AK074050]	chr7		GO:0016459(myosin complex)	GO:0003774(motor activity);GO:0005524(ATP binding)
A_23_P51213	NM_152372	MYOM3	NM_152372	Homo sapiens myomesin family, member 3 (MYOM3), mRNA [NM_152372]	chr1	GO:0007155(cell adhesion)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005515(protein binding)
A_23_P51215	NM_152372	MYOM3	NM_152372	Homo sapiens myomesin family, member 3 (MYOM3), mRNA [NM_152372]	chr1	GO:0007155(cell adhesion)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005515(protein binding)
A_23_P93938	ENST00000258775	NACAD		Homo sapiens mRNA for KIAA0363 gene, partial cds. [AB002361]	chr7	GO:0015031(protein transport)	GO:0005634(nucleus)	
A_32_P28365	NM_172164	NASP	NM_172164	Homo sapiens nuclear autoantigenic sperm protein (histone-binding) (NASP), transcript variant 1, mRNA [NM_172164]	chr1	GO:0001824(blastocyst development);GO:0006260(DNA replication);GO:0007049(cell cycle);GO:0008283(cell proliferation);GO:0015031(protein transport)	GO:0005634(nucleus)	GO:0005488(binding);GO:0005515(protein binding)
A_23_P52727	NM_182964	NAV2	NM_182964	Homo sapiens neuron navigator 2 (NAV2), transcript variant 1, mRNA [NM_182964]	chr11		GO:0005634(nucleus)	GO:0000166(nucleotide binding);GO:0004386(helicase activity);GO:0005524(ATP binding);GO:0016787(hydrolase activity);GO:0017111(nucleoside-triphosphatase activity)
A_23_P155815	NM_022346	NCAPG	NM_022346	Homo sapiens non-SMC condensin I complex, subunit G (NCAPG), mRNA [NM_022346]	chr4	GO:0007049(cell cycle);GO:0007067(mitosis);GO:0007076(mitotic chromosome condensation);GO:0051301(cell division)	GO:0005634(nucleus)	GO:0003674(molecular_function);GO:0005515(protein binding)
A_23_P415443	NM_015341	NCAPH	NM_015341	Homo sapiens non-SMC condensin I complex, subunit H (NCAPH), mRNA [NM_015341]	chr2	GO:0000278(mitotic cell cycle);GO:0007067(mitosis);GO:0007076(mitotic chromosome condensation);GO:0051301(cell division)	GO:0005634(nucleus)	
A_23_P50108	NM_006101	NDC80	NM_006101	Homo sapiens NDC80 homolog, kinetochore complex component (S. cerevisiae) (NDC80), mRNA [NM_006101]	chr18	GO:0000070(mitotic sister chromatid segregation);GO:0007049(cell cycle);GO:0007051(spindle organization and biogenesis);GO:0048015(phosphoinositide-mediated signaling);GO:0051301(cell division)	GO:0000775(chromosome, pericentric region);GO:0005634(nucleus)	GO:0005515(protein binding)
A_23_P73609	NM_000266	NDP	NM_000266	Homo sapiens Norrie disease (pseudoglioma) (NDP), mRNA [NM_000266]	chrX	GO:0001890(placenta development);GO:0007033(vacuole organization and biogenesis);GO:0007165(signal transduction);GO:0007267(cell-cell signaling);GO:0007399(nervous system development);GO:0007601(visual perception);GO:0007605(sensory perception of sound);GO:0008283(cell proliferation);GO:0050896(response to stimulus)	GO:0005615(extracellular space)	GO:0008083(growth factor activity)
A_23_P20494	NM_006096	NDRG1	NM_006096	Homo sapiens N-myc downstream regulated gene 1 (NDRG1), mRNA [NM_006096]	chr8	GO:0010038(response to metal ion);GO:0030154(cell differentiation)	GO:0005634(nucleus)	GO:0005515(protein binding)
A_23_P216355	NM_013432	NFKBIL2	NM_013432	Homo sapiens nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-like 2 (NFKBIL2), mRNA [NM_013432]	chr8	GO:0042994(cytoplasmic sequestering of transcription factor)	GO:0005737(cytoplasm)	GO:0003714(transcription corepressor activity);GO:0005488(binding);GO:0005515(protein binding)
A_23_P138693	NM_004808	NMT2	NM_004808	Homo sapiens N-myristoyltransferase 2 (NMT2), mRNA [NM_004808]	chr10	GO:0006499(N-terminal protein myristoylation);GO:0009249(protein-lipoylation)		GO:0004379(glycylpeptide N-tetradecanoyltransferase activity);GO:0008415(acyltransferase activity);GO:0016740(transferase activity)
A_23_P47148	NM_016931	NOX4	NM_016931	Homo sapiens NADPH oxidase 4 (NOX4), mRNA [NM_016931]	chr11	GO:0000902(cell morphogenesis);GO:0006118(electron transport);GO:0006800(oxygen and reactive oxygen species metabolic process);GO:0006954(inflammatory response);GO:0007569(cell aging);GO:0008285(negative regulation of cell proliferation);GO:0042554(superoxide release)	GO:0005634(nucleus);GO:0005783(endoplasmic reticulum);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0000166(nucleotide binding);GO:0005506(iron ion binding);GO:0009055(electron carrier activity);GO:0016174(NAD(P)H oxidase activity);GO:0019826(oxygen sensor activity);GO:0020037(heme binding);GO:0050660(FAD binding)
A_24_P739344	NM_016931	NOX4	NM_016931	Homo sapiens NADPH oxidase 4 (NOX4), mRNA [NM_016931]	chr11	GO:0000902(cell morphogenesis);GO:0006118(electron transport);GO:0006800(oxygen and reactive oxygen species metabolic process);GO:0006954(inflammatory response);GO:0007569(cell aging);GO:0008285(negative regulation of cell proliferation);GO:0042554(superoxide release)	GO:0005634(nucleus);GO:0005783(endoplasmic reticulum);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0000166(nucleotide binding);GO:0005506(iron ion binding);GO:0009055(electron carrier activity);GO:0016174(NAD(P)H oxidase activity);GO:0019826(oxygen sensor activity);GO:0020037(heme binding);GO:0050660(FAD binding)

A_23_P52298	NM_006993	NPM3	NM_006993	Homo sapiens nucleophosmin/nucleoplasmin, 3 (NPM3), mRNA [NM_006993]	chr10	GO:0006457(protein folding)	GO:0005634(nucleus)	GO:0003676(nucleic acid binding)
A_23_P213699	NM_013982	NRG2	NM_013982	Homo sapiens neuregulin 2 (NRG2), transcript variant 3, mRNA [NM_013982]	chr5	GO:0006916(anti-apoptosis);GO:0007165(signal transduction);GO:0007267(cell-cell signaling);GO:0009790(embryonic development)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0008083(growth factor activity)
A_23_P74349	NM_145697	NUF2	NM_145697	Homo sapiens NUF2, NDC80 kinetochore complex component, homolog (S. cerevisiae) (NUF2), transcript variant 1, mRNA [NM_145697]	chr1	GO:0007049(cell cycle);GO:0007059(chromosome segregation);GO:0007067(mitosis);GO:0051301(cell division)	GO:0000775(chromosome, pericentric region);GO:0005634(nucleus)	GO:0003674(molecular_function);GO:0005515(protein binding)
A_23_P7679	NM_153485	NUP155	NM_153485	Homo sapiens nucleoporin 155kDa (NUP155), transcript variant 1, mRNA [NM_153485]	chr5	GO:0006810(transport);GO:0006913(nucleocytoplasmic transport)	GO:0005634(nucleus);GO:0005643(nuclear pore)	GO:0005215(transporter activity);GO:0005487(nucleocytoplasmic transporter activity);GO:0017056(structural constituent of nuclear pore)
A_23_P47955	NM_006187	OAS3	NM_006187	Homo sapiens 2'-5'-oligoadenylate synthetase 3, 100kDa (OAS3), mRNA [NM_006187]	chr12	GO:0006139(nucleobase, nucleoside, nucleotide and nucleic acid metabolic process);GO:0006955(immune response)	GO:0005792(microsome)	GO:0003723(RNA binding);GO:0005524(ATP binding);GO:0016740(transferase activity);GO:0016779(nucleotidyltransferase activity)
A_23_P379614	NM_007280	OIP5	NM_007280	Homo sapiens Opa interacting protein 5 (OIP5), mRNA [NM_007280]	chr15	GO:0007154(cell communication)	GO:0005575(cellular_component)	GO:0005515(protein binding)
A_23_P100344	NM_014321	ORC6L	NM_014321	Homo sapiens origin recognition complex, subunit 6 like (yeast) (ORC6L), mRNA [NM_014321]	chr16	GO:0006260(DNA replication)	GO:0005634(nucleus);GO:0005664(nuclear origin of replication recognition complex)	GO:0003677(DNA binding);GO:0005515(protein binding)
A_23_P255331	NM_032623	OSAP	NM_032623	Homo sapiens ovary-specific acidic protein (OSAP), mRNA [NM_032623]	chr4			
A_23_P77415	NM_013370	OSGIN1	NM_013370	Homo sapiens oxidative stress induced growth inhibitor 1 (OSGIN1), transcript variant 1, mRNA [NM_013370]	chr16	GO:0007275(multicellular organismal development);GO:0030154(cell differentiation);GO:0030308(negative regulation of cell growth)	GO:0005575(cellular_component)	GO:0008083(growth factor activity)
A_23_P256244	AK096148	OXR1	AK096148	Homo sapiens cDNA FLJ38829 fis, clone MAMGL1000083, weakly similar to Drosophila melanogaster L82B (L82) mRNA. [AK096148]	chr8	GO:0006979(response to oxidative stress);GO:0016998(cell wall catabolic process)	GO:0005575(cellular_component);GO:0005739(mitochondrion)	GO:0003674(molecular_function)
A_23_P25354	NM_002562	P2RX7	NM_002562	Homo sapiens purinergic receptor P2X, ligand-gated ion channel, 7 (P2RX7), mRNA [NM_002562]	chr12	GO:0006811(ion transport);GO:0007165(signal transduction)	GO:0005887(integral to plasma membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0004872(receptor activity);GO:0004931(ATP-gated cation channel activity);GO:0005216(ion channel activity);GO:0005524(ATP binding)
A_23_P18966	NM_001017973	P4HA2	NM_001017973	Homo sapiens procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), alpha polypeptide II (P4HA2), transcript variant 2, mRNA [NM_001017973]	chr5	GO:0018401(peptidyl-proline hydroxylation to 4-hydroxy-L-proline);GO:0019538(protein metabolic process)	GO:0005783(endoplasmic reticulum)	GO:0004656(procollagen-proline 4-dioxygenase activity);GO:0005506(iron ion binding);GO:0005515(protein binding);GO:0009055(electron carrier activity);GO:0016702(oxidoreductase activity, acting on single donors with incorporation of molecular oxygen, incorporation of two atoms of oxygen);GO:0016706(oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, 2-oxoglutarate as one donor, and incorporation of one atom each of oxygen into both donors);GO:0031418(L-ascorbic acid binding);GO:0046872(metal ion binding)
A_23_P41280	NM_006452	PAICS	NM_006452	Homo sapiens phosphoribosylaminoimidazole carboxylase, phosphoribosylaminoimidazole succinocarboxamide synthetase (PAICS), transcript variant 2, mRNA [NM_006452]	chr4	GO:0006164(purine nucleotide biosynthetic process);GO:0006189('de novo' IMP biosynthetic process);GO:0009113(purine base biosynthetic process)	GO:0009320(phosphoribosylaminoimidazole carboxylase complex)	GO:0003824(catalytic activity);GO:0004638(phosphoribosylaminoimidazole carboxylase activity);GO:0004639(phosphoribosylaminoimidazolesuccinocarboxamide synthase activity);GO:0005524(ATP binding);GO:0016829(lyase activity);GO:0016874(ligase activity);GO:0042802(identical protein binding)
A_23_P208991	NM_002579	PALM	NM_002579	Homo sapiens paralemmin (PALM), transcript variant 1, mRNA [NM_002579]	chr19	GO:0006928(cell motility);GO:0008360(regulation of cell shape)	GO:0005886(plasma membrane);GO:0005887(integral to plasma membrane);GO:0016023(cytoplasmic membrane-bound vesicle)	
A_23_P155162	NM_052839	PANX2	NM_052839	Homo sapiens pannexin 2 (PANX2), mRNA [NM_052839]	chr22		GO:0005921(gap junction);GO:0016020(membrane);GO:0016021(integral to membrane)	
A_24_P299911	NM_015148	PASK	NM_015148	Homo sapiens PAS domain containing serine/threonine kinase (PASK), mRNA [NM_015148]	chr2	GO:0006355(regulation of transcription, DNA-dependent);GO:0006468(protein amino acid phosphorylation);GO:0007165(signal transduction)		GO:0000166(nucleotide binding);GO:0004674(protein serine/threonine kinase activity);GO:0004871(signal transducer activity);GO:0005524(ATP binding);GO:0016740(transferase activity);GO:0042802(identical protein binding)
A_32_P62997	NM_018492	PBK	NM_018492	Homo sapiens PDZ binding kinase (PBK), mRNA [NM_018492]	chr8	GO:0006468(protein amino acid phosphorylation);GO:0007067(mitosis)	GO:0005575(cellular_component)	GO:0000166(nucleotide binding);GO:0004674(protein serine/threonine kinase activity);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0016740(transferase activity)
A_23_P158851	NM_032961	PCDH10	NM_032961	Homo sapiens protocadherin 10 (PCDH10), transcript variant 1, mRNA [NM_032961]	chr4	GO:0007155(cell adhesion);GO:0007156(homophilic cell adhesion)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005509(calcium ion binding);GO:0005515(protein binding)
A_24_P419039	NM_020766	PCDH19	NM_020766	Homo sapiens protocadherin 19 (PCDH19), mRNA [NM_020766]	chrX	GO:0007155(cell adhesion);GO:0007156(homophilic cell adhesion)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005509(calcium ion binding);GO:0005515(protein binding)
A_23_P310921	NM_002589	PCDH7	NM_002589	Homo sapiens protocadherin 7 (PCDH7), transcript variant a, mRNA [NM_002589]	chr4	GO:0007155(cell adhesion);GO:0007156(homophilic cell adhesion)	GO:0005886(plasma membrane);GO:0005887(integral to plasma membrane)	GO:0005509(calcium ion binding);GO:0005515(protein binding)

A_23_P28886	NM_002592	PCNA	NM_002592	Homo sapiens proliferating cell nuclear antigen (PCNA), transcript variant 1, mRNA [NM_002592]	chr20	GO:0000074(regulation of progression through cell cycle);GO:0006260(DNA replication);GO:0006275(regulation of DNA replication);GO:0006281(DNA repair);GO:0006287(base-excision repair, gap-filling);GO:0006886(intracellular protein transport);GO:0008283(cell proliferation);GO:0048015(phosphoinositide-mediated signaling)	GO:0000307(cyclin-dependent protein kinase holoenzyme complex);GO:0005634(nucleus);GO:0005652(nuclear lamina);GO:0005663(DNA replication factor C complex)	GO:0003677(DNA binding);GO:0005515(protein binding);GO:0030337(DNA polymerase processivity factor activity)
A_23_P65532	NM_021255	PELI2	NM_021255	Homo sapiens pellino homolog 2 (Drosophila) (PELI2), mRNA [NM_021255]	chr14		GO:0005829(cytosol);GO:0016020(membrane);GO:0043234(protein complex)	GO:0005515(protein binding)
A_23_P402610	NM_012393	PFAS	NM_012393	Homo sapiens phosphoribosylformylglycinamidine synthase (FGAR amidotransferase) (PFAS), mRNA [NM_012393]	chr17	GO:0006164(purine nucleotide biosynthetic process);GO:0006189('de novo' IMP biosynthetic process);GO:0006541(glutamine metabolic process)	GO:0005737(cytoplasm)	GO:0000166(nucleotide binding);GO:0004642(phosphoribosylformylglycinamidine synthase activity);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0016874(ligase activity)
A_23_P21436	NM_015651	PHF19	NM_015651	Homo sapiens PHD finger protein 19 (PHF19), transcript variant 1, mRNA [NM_015651]	chr9			GO:0003676(nucleic acid binding);GO:0005515(protein binding);GO:0008270(zinc ion binding)
A_24_P105102	NM_182687	PKMYT1	NM_182687	Homo sapiens protein kinase, membrane associated tyrosine/threonine 1 (PKMYT1), transcript variant 2, mRNA [NM_182687]	chr16	GO:0000079(regulation of cyclin-dependent protein kinase activity);GO:0006468(protein amino acid phosphorylation);GO:0007049(cell cycle);GO:0007088(regulation of mitosis)	GO:0005624(membrane fraction);GO:0005783(endoplasmic reticulum);GO:0005794(Golgi apparatus);GO:0016020(membrane)	GO:0000166(nucleotide binding);GO:0004674(protein serine/threonine kinase activity);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0016740(transferase activity)
A_23_P106675	NM_002661	PLCG2	NM_002661	Homo sapiens phospholipase C, gamma 2 (phosphatidylinositol-specific) (PLCG2), mRNA [NM_002661]	chr16	GO:0006644(phospholipid metabolic process);GO:0007166(cell surface receptor linked signal transduction);GO:0007242(intracellular signaling cascade);GO:0016042(lipid catabolic process)		GO:0004435(phosphoinositide phospholipase C activity);GO:0004871(signal transducer activity);GO:0005509(calcium ion binding);GO:0005515(protein binding);GO:0016787(hydrolase activity)
A_24_P313504	NM_005030	PLK1	NM_005030	Homo sapiens polo-like kinase 1 (Drosophila) (PLK1), mRNA [NM_005030]	chr16	GO:0000074(regulation of progression through cell cycle);GO:0006468(protein amino acid phosphorylation);GO:0007067(mitosis);GO:0008283(cell proliferation)	GO:0005634(nucleus);GO:0005813(centrosome)	GO:0000166(nucleotide binding);GO:0004674(protein serine/threonine kinase activity);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0016740(transferase activity)
A_23_P155969	NM_014264	PLK4	NM_014264	Homo sapiens polo-like kinase 4 (Drosophila) (PLK4), mRNA [NM_014264]	chr4	GO:0000074(regulation of progression through cell cycle);GO:0006468(protein amino acid phosphorylation)		GO:0000166(nucleotide binding);GO:0004674(protein serine/threonine kinase activity);GO:0004713(protein-tyrosine kinase activity);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0016740(transferase activity)
A_24_P912925	NM_014264	PLK4	NM_014264	Homo sapiens polo-like kinase 4 (Drosophila) (PLK4), mRNA [NM_014264]	chr4	GO:0000074(regulation of progression through cell cycle);GO:0006468(protein amino acid phosphorylation)		GO:0000166(nucleotide binding);GO:0004674(protein serine/threonine kinase activity);GO:0004713(protein-tyrosine kinase activity);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0016740(transferase activity)
A_24_P389415	NM_007257	PNMA2	NM_007257	Homo sapiens paraneoplastic antigen MA2 (PNMA2), mRNA [NM_007257]	chr8		GO:0005634(nucleus)	GO:0005515(protein binding)
A_23_P215060	NM_005397	PODXL	NM_005397	Homo sapiens podocalyxin-like (PODXL), transcript variant 2, mRNA [NM_005397]	chr7		GO:0005887(integral to plasma membrane);GO:0016020(membrane)	
A_32_P1701	NM_016937	POLA1	NM_016937	Homo sapiens polymerase (DNA directed), alpha 1 (POLA1), mRNA [NM_016937]	chrX	GO:0000084(S phase of mitotic cell cycle);GO:0000731(DNA synthesis during DNA repair);GO:0006139(nucleobase, nucleoside, nucleotide and nucleic acid metabolic process);GO:0006270(DNA replication initiation);GO:0006272(leading strand elongation);GO:0006273(lagging strand elongation);GO:0006303(double-strand break repair via nonhomologous end joining);GO:0008283(cell proliferation);GO:0009268(response to pH);GO:0009615(response to virus)	GO:0000785(chromatin);GO:0005634(nucleus);GO:0005635(nuclear envelope);GO:0005654(nucleoplasm);GO:0005658(alpha DNA polymerase:primase complex);GO:0005730(nucleolus);GO:0016363(nuclear matrix)	GO:0000166(nucleotide binding);GO:0003677(DNA binding);GO:0003682(chromatin binding);GO:0003889(alpha DNA polymerase activity);GO:0003896(DNA primase activity);GO:0005515(protein binding);GO:0005529(sugar binding);GO:0008270(zinc ion binding);GO:0016740(transferase activity);GO:0046872(metal ion binding);GO:0046982(protein heterodimerization activity)
A_23_P161615	NM_002689	POLA2	NM_002689	Homo sapiens polymerase (DNA directed), alpha 2 (70kD subunit) (POLA2), mRNA [NM_002689]	chr11	GO:0000060(protein import into nucleus, translocation);GO:0006260(DNA replication)	GO:0005634(nucleus);GO:0005658(alpha DNA polymerase:primase complex)	GO:0003674(molecular_function);GO:0003677(DNA binding);GO:0003887(DNA-directed DNA polymerase activity);GO:0005515(protein binding);GO:0046982(protein heterodimerization activity)
A_23_P163099	NM_002692	POLE2	NM_002692	Homo sapiens polymerase (DNA directed), epsilon 2 (p59 subunit) (POLE2), mRNA [NM_002692]	chr14	GO:0006260(DNA replication);GO:0006281(DNA repair)	GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0003893(epsilon DNA polymerase activity);GO:0016740(transferase activity)
A_23_P218827	NM_199420	POLQ	NM_199420	Homo sapiens polymerase (DNA directed), theta (POLQ), mRNA [NM_199420]	chr3	GO:0006260(DNA replication);GO:0006281(DNA repair)	GO:0005654(nucleoplasm)	GO:0000166(nucleotide binding);GO:0003677(DNA binding);GO:0003684(damaged DNA binding);GO:0003887(DNA-directed DNA polymerase activity);GO:0005524(ATP binding);GO:0008026(ATP-dependent helicase activity);GO:0016740(transferase activity)
A_23_P41942	NM_006467	POLR3G	NM_006467	Homo sapiens polymerase (RNA) III (DNA directed) polypeptide G (32kD) (POLR3G), mRNA [NM_006467]	chr5	GO:0006350(transcription);GO:0006359(regulation of transcription from RNA polymerase III promoter)	GO:0005634(nucleus);GO:0005666(DNA-directed RNA polymerase III complex)	GO:0003899(DNA-directed RNA polymerase activity);GO:0016740(transferase activity)
A_24_P13533	NM_203467	PPIL5	NM_203467	Homo sapiens peptidylprolyl isomerase (cyclophilin)-like 5 (PPIL5), transcript variant 3, mRNA [NM_203467]	chr14			GO:0005515(protein binding)
A_23_P206059	NM_003981	PRC1	NM_003981	Homo sapiens protein regulator of cytokinesis 1 (PRC1), transcript variant 1, mRNA [NM_003981]	chr15	GO:0000022(mitotic spindle elongation);GO:0000910(cytokinesis);GO:0007049(cell cycle)	GO:0005634(nucleus);GO:0005876(spindle microtubule)	GO:0005515(protein binding)

A_23_P25019	NM_000946	PRIM1	NM_000946	Homo sapiens primase, polypeptide 1, 49kDa (PRIM1), mRNA [NM_000946]	chr12	GO:0006260(DNA replication);GO:0006269(DNA replication, synthesis of RNA primer)	GO:0005658(alpha DNA polymerase:primase complex)	GO:0003896(DNA primase activity);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0016740(transferase activity);GO:0046872(metal ion binding)
A_23_P44139	NM_000947	PRIM2A	NM_000947	Homo sapiens primase, polypeptide 2A, 58kDa (PRIM2A), mRNA [NM_000947]	chr6	GO:0006260(DNA replication);GO:0006269(DNA replication, synthesis of RNA primer)	GO:0005658(alpha DNA polymerase:primase complex)	GO:0003677(DNA binding);GO:0003896(DNA primase activity);GO:0016740(transferase activity)
A_23_P20392	NM_015310	PSD3	NM_015310	Homo sapiens pleckstrin and Sec7 domain containing 3 (PSD3), transcript variant 1, mRNA [NM_015310]	chr8		GO:0005622(intracellular)	GO:0005086(ARF guanyl-nucleotide exchange factor activity)
A_24_P18146	NM_015310	PSD3	NM_015310	Homo sapiens pleckstrin and Sec7 domain containing 3 (PSD3), transcript variant 1, mRNA [NM_015310]	chr8		GO:0005622(intracellular)	GO:0005086(ARF guanyl-nucleotide exchange factor activity)
A_23_P5103	NM_213633	PSG4	NM_213633	Homo sapiens pregnancy specific beta-1-glycoprotein 4 (PSG4), transcript variant 2, mRNA [NM_213633]	chr19	GO:0006952(defense response);GO:0007565(pregnancy)	GO:0005576(extracellular region);GO:0005615(extracellular space);GO:0016021(integral to membrane)	
A_24_P287941	NM_013290	PSMC3IP	NM_013290	Homo sapiens PSMC3 interacting protein (PSMC3IP), transcript variant 1, mRNA [NM_013290]	chr17	GO:0008150(biological_process)	GO:0005575(cellular_component)	GO:0003674(molecular_function);GO:0005515(protein binding)
A_23_P46539	NM_032636	PSRC1	NM_032636	Homo sapiens proline/serine-rich coiled-coil 1 (PSRC1), transcript variant 1, mRNA [NM_032636]	chr1			
A_23_P208119	NM_024430	PSTPIP2	NM_024430	Homo sapiens proline-serine-threonine phosphatase interacting protein 2 (PSTPIP2), mRNA [NM_024430]	chr18			
A_23_P149345	NM_015967	PTPN22	NM_015967	Homo sapiens protein tyrosine phosphatase, non-receptor type 22 (lymphoid) (PTPN22), transcript variant 1, mRNA [NM_015967]	chr1	GO:0006470(protein amino acid dephosphorylation);GO:0007165(signal transduction);GO:0007275(multicellular organismal development)		GO:0004725(protein tyrosine phosphatase activity);GO:0005515(protein binding);GO:0016787(hydrolase activity);GO:0016791(phosphoric monoester hydrolase activity)
A_23_P7636	NM_004219	PTTG1	NM_004219	Homo sapiens pituitary tumor-transforming 1 (PTTG1), mRNA [NM_004219]	chr5	GO:0006259(DNA metabolic process);GO:0006281(DNA repair);GO:0006366(transcription from RNA polymerase II promoter);GO:0007049(cell cycle);GO:0007059(chromosome segregation);GO:0007067(mitosis);GO:0007283(spermatogenesis);GO:0051276(chromosome organization and biogenesis);GO:0051301(cell division)	GO:0005575(cellular_component);GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0003674(molecular_function);GO:0003700(transcription factor activity);GO:0004869(cysteine protease inhibitor activity);GO:0005515(protein binding)
A_23_P18579	NM_006607	PTTG2	NM_006607	Homo sapiens pituitary tumor-transforming 2 (PTTG2), mRNA [NM_006607]	chr4	GO:0006259(DNA metabolic process);GO:0051276(chromosome organization and biogenesis)	GO:0005575(cellular_component);GO:0005634(nucleus);GO:0005737(cytoplasm)	GO:0003674(molecular_function)
A_23_P60016	NR_002734	PTTG3	NR_002734	Homo sapiens pituitary tumor-transforming 3 (PTTG3) on chromosome 8 [NR_002734]	chr8	GO:0006259(DNA metabolic process);GO:0051276(chromosome organization and biogenesis)	GO:0005634(nucleus);GO:0005737(cytoplasm)	
A_23_P121064	NM_002852	PTX3	NM_002852	**Homo sapiens pentraxin-related gene**, rapidly induced by IL-1 beta (PTX3), mRNA [NM_002852]	**chr3**	**GO:0001878(response to yeast);GO:0006954(inflammatory** response);GO:0008228(opsonization);GO:0045429(positive regulation of nitric oxide biosynthetic process);GO:0050766(positive regulation of phagocytosis)	**GO:0005576(extracellular region)**	**GO:0001872(zymosan binding)**
A_32_P180920	NM_175623	RAB3IP	NM_175623	Homo sapiens RAB3A interacting protein (rabin3) (RAB3IP), transcript variant alpha 2, mRNA [NM_175623]	chr12	GO:0015031(protein transport)	GO:0005634(nucleus);GO:0005829(cytosol)	GO:0005096(GTPase activator activity);GO:0005515(protein binding)
A_23_P65110	NM_013277	RACGAP1	NM_013277	Homo sapiens Rac GTPase activating protein 1 (RACGAP1), mRNA [NM_013277]	chr12	GO:0000910(cytokinesis);GO:0000915(cytokinesis, contractile ring formation);GO:0007049(cell cycle);GO:0007108(cytokinesis, initiation of separation);GO:0007165(signal transduction);GO:0007242(intracellular signaling cascade);GO:0007283(spermatogenesis);GO:0007405(neuroblast proliferation);GO:0009790(embryonic development)	GO:0005622(intracellular);GO:0005634(nucleus);GO:0005874(microtubule)	GO:0005096(GTPase activator activity);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0019992(diacylglycerol binding);GO:0043014(alpha-tubulin binding);GO:0043015(gamma-tubulin binding);GO:0046872(metal ion binding);GO:0048487(beta-tubulin binding)
A_23_P65041	AF334184	RACGAP1P	AF334184	Homo sapiens FKSG42 (FKSG42) mRNA, complete cds. [AF334184]	chr12	GO:0007165(signal transduction)	GO:0005622(intracellular)	
A_23_P88731	NM_002875	RAD51	NM_002875	Homo sapiens RAD51 homolog (RecA homolog, E. coli) (S. cerevisiae) (RAD51), transcript variant 1, mRNA [NM_002875]	chr15	GO:0000724(double-strand break repair via homologous recombination);GO:0006268(DNA unwinding during replication);GO:0006281(DNA repair);GO:0006312(mitotic recombination);GO:0007126(meiosis);GO:0007131(meiotic recombination);GO:0051106(positive regulation of DNA ligation);GO:0051260(protein homooligomerization)	GO:0000795(synaptonemal complex);GO:0005622(intracellular);GO:0005634(nucleus)	GO:0000150(recombinase activity);GO:0000166(nucleotide binding);GO:0003684(damaged DNA binding);GO:0003690(double-stranded DNA binding);GO:0003697(single-stranded DNA binding);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0008094(DNA-dependent ATPase activity);GO:0016887(ATPase activity);GO:0017111(nucleoside-triphosphatase activity);GO:0042802(identical protein binding);GO:0043142(single-stranded DNA-dependent ATPase activity)
A_23_P99292	NM_006479	RAD51AP1	NM_006479	Homo sapiens RAD51 associated protein 1 (RAD51AP1), mRNA [NM_006479]	chr12	GO:0000724(double-strand break repair via homologous recombination);GO:0006281(DNA repair)	GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0003690(double-stranded DNA binding);GO:0003697(single-stranded DNA binding);GO:0003723(RNA binding);GO:0005515(protein binding)

A_23_P74115	NM_003579	RAD54L	NM_003579	Homo sapiens RAD54-like (S. cerevisiae) (RAD54L), mRNA [NM_003579]	chr1	GO:0006281(DNA repair);GO:0006310(DNA recombination);GO:0007126(meiosis)	GO:0005634(nucleus)	GO:0000166(nucleotide binding);GO:0003677(DNA binding);GO:0004386(helicase activity);GO:0005524(ATP binding);GO:0016787(hydrolase activity)
A_23_P333420	NM_002883	RANGAP1	NM_002883	Homo sapiens Ran GTPase activating protein 1 (RANGAP1), mRNA [NM_002883]	chr22	GO:0007165(signal transduction)	GO:0005625(soluble fraction);GO:0005643(nuclear pore);GO:0005737(cytoplasm);GO:0048471(perinuclear region of cytoplasm)	GO:0005096(GTPase activator activity);GO:0005098(Ran GTPase activator activity);GO:0005515(protein binding)
A_24_P3249	NM_000965	RARB	NM_000965	Homo sapiens retinoic acid receptor, beta (RARB), transcript variant 1, mRNA [NM_000965]	chr3	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0007165(signal transduction)	GO:0005575(cellular_component);GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0003707(steroid hormone receptor activity);GO:0003708(retinoic acid receptor activity);GO:0004872(receptor activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P28733	NM_002895	RBL1	NM_002895	Homo sapiens retinoblastoma-like 1 (p107) (RBL1), transcript variant 1, mRNA [NM_002895]	chr20	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0007049(cell cycle);GO:0016568(chromatin modification);GO:0045786(negative regulation of progression through cell cycle)	GO:0005634(nucleus)	GO:0005515(protein binding)
A_24_P276102	NM_183404	RBL1	NM_183404	Homo sapiens retinoblastoma-like 1 (p107) (RBL1), transcript variant 2, mRNA [NM_183404]	chr20	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0007049(cell cycle);GO:0016568(chromatin modification);GO:0045786(negative regulation of progression through cell cycle)	GO:0005634(nucleus)	GO:0005515(protein binding)
A_23_P167812	NM_153020	RBM24	NM_153020	Homo sapiens RNA binding motif protein 24 (RBM24), mRNA [NM_153020]	chr6	GO:0016068(type I hypersensitivity)	GO:0005634(nucleus)	GO:0000166(nucleotide binding);GO:0003723(RNA binding)
A_24_P252057	NM_153020	RBM24	NM_153020	Homo sapiens RNA binding motif protein 24 (RBM24), mRNA [NM_153020]	chr6	GO:0016068(type I hypersensitivity)	GO:0005634(nucleus)	GO:0000166(nucleotide binding);GO:0003723(RNA binding)
A_23_P100056	NM_194272	RBPMS2	NM_194272	Homo sapiens RNA binding protein with multiple splicing 2 (RBPMS2), mRNA [NM_194272]	chr15			GO:0000166(nucleotide binding);GO:0003676(nucleic acid binding)
A_23_P141447	NM_145654	RDM1	NM_145654	Homo sapiens RAD52 motif 1 (RDM1), transcript variant 1, mRNA [NM_145654]	chr17			
A_23_P14193	NM_002915	RFC3	NM_002915	Homo sapiens replication factor C (activator 1) 3, 38kDa (RFC3), transcript variant 1, mRNA [NM_002915]	chr13	GO:0006260(DNA replication);GO:0006271(DNA strand elongation during DNA replication)	GO:0005634(nucleus);GO:0005663(DNA replication factor C complex)	GO:0000166(nucleotide binding);GO:0003677(DNA binding);GO:0003887(DNA-directed DNA polymerase activity);GO:0005515(protein binding);GO:0008047(enzyme activator activity);GO:0017111(nucleoside-triphosphatase activity)
A_23_P118122	NM_003834	RGS11	NM_003834	Homo sapiens regulator of G-protein signalling 11 (RGS11), transcript variant 2, mRNA [NM_003834]	chr16	GO:0007186(G-protein coupled receptor protein signaling pathway);GO:0007242(intracellular signaling cascade);GO:0008277(regulation of G-protein coupled receptor protein signaling pathway);GO:0009968(negative regulation of signal transduction)	GO:0005834(heterotrimeric G-protein complex)	GO:0004871(signal transducer activity);GO:0005096(GTPase activator activity)
A_23_P200737	NM_005613	RGS4	NM_005613	Homo sapiens regulator of G-protein signalling 4 (RGS4), mRNA [NM_005613]	chr1	GO:0000188(inactivation of MAPK activity);GO:0008277(regulation of G-protein coupled receptor protein signaling pathway);GO:0009968(negative regulation of signal transduction)		GO:0004871(signal transducer activity);GO:0005096(GTPase activator activity);GO:0005516(calmodulin binding)
A_23_P66881	NM_003835	RGS9	NM_003835	Homo sapiens regulator of G-protein signalling 9 (RGS9), transcript variant 1, mRNA [NM_003835]	chr17	GO:0007242(intracellular signaling cascade);GO:0007601(visual perception);GO:0008277(regulation of G-protein coupled receptor protein signaling pathway);GO:0009968(negative regulation of signal transduction);GO:0050896(response to stimulus)	GO:0005834(heterotrimeric G-protein complex)	GO:0004871(signal transducer activity);GO:0005096(GTPase activator activity)
A_23_P166526	NM_015653	RIBC2	NM_015653	Homo sapiens RIB43A domain with coiled-coils 2 (RIBC2), mRNA [NM_015653]	chr22			
A_23_P164826	NM_006397	RNASEH2A	NM_006397	Homo sapiens ribonuclease H2, subunit A (RNASEH2A), mRNA [NM_006397]	chr19	GO:0006260(DNA replication);GO:0006401(RNA catabolic process)	GO:0005634(nucleus)	GO:0003723(RNA binding);GO:0004519(endonuclease activity);GO:0004523(ribonuclease H activity);GO:0004540(ribonuclease activity);GO:0016787(hydrolase activity);GO:0046872(metal ion binding)
A_23_P29594	NM_052969	RPL39L	NM_052969	Homo sapiens ribosomal protein L39-like (RPL39L), mRNA [NM_052969]	chr3	GO:0006412(translation);GO:0007283(spermatogenesis)	GO:0005622(intracellular);GO:0005840(ribosome);GO:0005842(cytosolic large ribosomal subunit (sensu Eukaryota))	GO:0003735(structural constituent of ribosome)
A_23_P87351	NM_001033	RRM1	NM_001033	Homo sapiens ribonucleotide reductase M1 polypeptide (RRM1), mRNA [NM_001033]	chr11	GO:0006260(DNA replication)	GO:0005971(ribonucleoside-diphosphate reductase complex)	GO:0000166(nucleotide binding);GO:0004748(ribonucleoside-diphosphate reductase activity);GO:0005524(ATP binding);GO:0016491(oxidoreductase activity)
A_24_P234196	NM_001034	RRM2	NM_001034	Homo sapiens ribonucleotide reductase M2 polypeptide (RRM2), mRNA [NM_001034]	chr2	GO:0006260(DNA replication);GO:0009186(deoxyribonucleoside diphosphate metabolic process)	GO:0005737(cytoplasm)	GO:0004748(ribonucleoside-diphosphate reductase activity);GO:0005506(iron ion binding);GO:0005515(protein binding);GO:0016491(oxidoreductase activity)
A_23_P111402	NM_032784	RSPO3	NM_032784	Homo sapiens R-spondin 3 homolog (Xenopus laevis) (RSPO3), mRNA [NM_032784]	chr6	GO:0006118(electron transport);GO:0016055(Wnt receptor signaling pathway);GO:0050896(response to stimulus)		GO:0008201(heparin binding);GO:0009055(electron carrier activity)
A_23_P132175	NM_023004	RTN4R	NM_023004	Homo sapiens reticulon 4 receptor (RTN4R), mRNA [NM_023004]	chr22	GO:0007409(axonogenesis)	GO:0005783(endoplasmic reticulum);GO:0005886(plasma membrane)	GO:0004872(receptor activity);GO:0005515(protein binding);GO:0048503(GPI anchor binding)

A_23_P372888	NM_006918	SC5DL	NM_006918	Homo sapiens sterol-C5-desaturase (ERG3 delta-5-desaturase homolog, S. cerevisiae)-like (SC5DL), transcript variant 1, mRNA [NM_006918]	chr11	GO:0006629(lipid metabolic process);GO:0008152(metabolic process);GO:0016126(sterol biosynthetic process)	GO:0005783(endoplasmic reticulum);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0000248(C-5 sterol desaturase activity);GO:0005506(iron ion binding);GO:0016491(oxidoreductase activity)
A_23_P72668	NM_004657	SDPR	NM_004657	Homo sapiens serum deprivation response (phosphatidylserine binding protein) (SDPR), mRNA [NM_004657]	chr2		GO:0005624(membrane fraction);GO:0005829(cytosol);GO:0005901(caveola)	GO:0001786(phosphatidylserine binding);GO:0005515(protein binding)
A_23_P317591	NM_006080	SEMA3A	NM_006080	Homo sapiens sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3A (SEMA3A), mRNA [NM_006080]	chr7	GO:0007275(multicellular organismal development);GO:0007399(nervous system development);GO:0007411(axon guidance);GO:0030154(cell differentiation);GO:0050919(negative chemotaxis)	GO:0005576(extracellular region)	GO:0045499(chemorepellant activity)
A_24_P192301	NM_006080	SEMA3A	NM_006080	Homo sapiens sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3A (SEMA3A), mRNA [NM_006080]	chr7	GO:0007275(multicellular organismal development);GO:0007399(nervous system development);GO:0007411(axon guidance);GO:0030154(cell differentiation);GO:0050919(negative chemotaxis)	GO:0005576(extracellular region)	GO:0045499(chemorepellant activity)
A_23_P420442	NM_153618	SEMA6D	NM_153618	Homo sapiens sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D (SEMA6D), transcript variant 4, mRNA [NM_153618]	chr15	GO:0007275(multicellular organismal development);GO:0007399(nervous system development);GO:0030154(cell differentiation)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0004872(receptor activity)
A_23_P121926	NM_005410	SEPP1	NM_005410	Homo sapiens selenoprotein P, plasma, 1 (SEPP1), mRNA [NM_005410]	chr5	GO:0001887(selenium metabolic process);GO:0006979(response to oxidative stress);GO:0007420(brain development);GO:0007626(locomotory behavior);GO:0009791(post-embryonic development);GO:0019953(sexual reproduction);GO:0040007(growth)	GO:0005576(extracellular region);GO:0005615(extracellular space)	GO:0008430(selenium binding)
A_23_P6335	NM_000185	SERPIND1	NM_000185	Homo sapiens serpin peptidase inhibitor, clade D (heparin cofactor), member 1 (SERPIND1), mRNA [NM_000185]	chr22	GO:0006935(chemotaxis);GO:0007596(blood coagulation)	GO:0005576(extracellular region)	GO:0004867(serine-type endopeptidase inhibitor activity);GO:0008201(heparin binding)
A_23_P361448	NM_144665	SESN3	NM_144665	Homo sapiens sestrin 3 (SESN3), mRNA [NM_144665]	chr11	GO:0007050(cell cycle arrest)	GO:0005634(nucleus)	
A_24_P175612	NM_178858	SFXN2	NM_178858	Homo sapiens sideroflexin 2 (SFXN2), mRNA [NM_178858]	chr10	GO:0006812(cation transport);GO:0006826(iron ion transport)	GO:0005739(mitochondrion);GO:0005743(mitochondrial inner membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005506(iron ion binding);GO:0008324(cation transporter activity)
A_23_P29723	NM_001012410	SGOL1	NM_001012410	Homo sapiens shugoshin-like 1 (S. pombe) (SGOL1), transcript variant A2, mRNA [NM_001012410]	chr3	GO:0007049(cell cycle);GO:0007067(mitosis);GO:0045132(meiotic chromosome segregation);GO:0051301(cell division)	GO:0000775(chromosome, pericentric region);GO:0005634(nucleus)	GO:0005515(protein binding)
A_24_P225970	NM_001012409	SGOL1	NM_001012409	Homo sapiens shugoshin-like 1 (S. pombe) (SGOL1), transcript variant A1, mRNA [NM_001012409]	chr3	GO:0007049(cell cycle);GO:0007067(mitosis);GO:0045132(meiotic chromosome segregation);GO:0051301(cell division)	GO:0000775(chromosome, pericentric region);GO:0005634(nucleus)	GO:0005515(protein binding)
A_23_P411335	NM_152524	SGOL2	NM_152524	Homo sapiens shugoshin-like 2 (S. pombe) (SGOL2), mRNA [NM_152524]	chr2	GO:0007049(cell cycle);GO:0007059(chromosome segregation);GO:0051301(cell division)	GO:0000775(chromosome, pericentric region);GO:0005634(nucleus)	GO:0005515(protein binding)
A_23_P116642	NM_133489	SLC26A10	NM_133489	Homo sapiens solute carrier family 26, member 10 (SLC26A10), mRNA [NM_133489]	chr12	GO:0006810(transport);GO:0035023(regulation of Rho protein signal transduction)	GO:0005622(intracellular);GO:0016021(integral to membrane)	GO:0005089(Rho guanyl-nucleotide exchange factor activity);GO:0005215(transporter activity)
A_23_P133694	NM_004955	SLC29A1	NM_004955	Homo sapiens solute carrier family 29 (nucleoside transporters), member 1 (SLC29A1), nuclear gene encoding mitochondrial protein, transcript variant 5, mRNA [NM_004955]	chr6	GO:0006139(nucleobase, nucleoside, nucleotide and nucleic acid metabolic process);GO:0006810(transport);GO:0015858(nucleoside transport)	GO:0005624(membrane fraction);GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0005337(nucleoside transporter activity);GO:0005515(protein binding)
A_23_P204801	NM_032148	SLC41A2	NM_032148	Homo sapiens solute carrier family 41, member 2 (SLC41A2), mRNA [NM_032148]	chr12	GO:0006812(cation transport)		GO:0008324(cation transporter activity)
A_23_P358548	NM_199329	SLC43A3	NM_199329	Homo sapiens solute carrier family 43, member 3 (SLC43A3), mRNA [NM_199329]	chr11			
A_24_P406986	NM_199329	SLC43A3	NM_199329	Homo sapiens solute carrier family 43, member 3 (SLC43A3), mRNA [NM_199329]	chr11			
A_32_P165477	NM_014331	SLC7A11	NM_014331	Homo sapiens solute carrier family 7, (cationic amino acid transporter, y+ system) member 11 (SLC7A11), mRNA [NM_014331]	chr4	GO:0006461(protein complex assembly);GO:0006810(transport);GO:0006865(amino acid transport)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0015171(amino acid transporter activity);GO:0015327(cystine:glutamate antiporter activity);GO:0015359(amino acid permease activity)
A_32_P42684	NM_014331	SLC7A11	NM_014331	Homo sapiens solute carrier family 7, (cationic amino acid transporter, y+ system) member 11 (SLC7A11), mRNA [NM_014331]	chr4	GO:0006461(protein complex assembly);GO:0006810(transport);GO:0006865(amino acid transport)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0015171(amino acid transporter activity);GO:0015327(cystine:glutamate antiporter activity);GO:0015359(amino acid permease activity)
A_23_P253451	NM_020949	SLC7A14	NM_020949	Homo sapiens solute carrier family 7 (cationic amino acid transporter, y+ system), member 14 (SLC7A14), mRNA [NM_020949]	chr3	GO:0006810(transport);GO:0006865(amino acid transport)	GO:0016020(membrane)	GO:0015171(amino acid transporter activity)

A_23_P359091	U68019	SMAD3	U68019	Homo sapiens mad protein homolog (hMAD-3) mRNA, complete cds. [U68019]	chr15	GO:0000122(negative regulation of transcription from RNA polymerase II promoter);GO:0001707(mesoderm formation);GO:0006350(transcription);GO:0006366(transcription from RNA polymerase II promoter);GO:0016202(regulation of striated muscle development);GO:0017015(regulation of transforming growth factor beta receptor signaling pathway);GO:0042110(T cell activation);GO:0045944(positive regulation of transcription from RNA polymerase II promoter);GO:0048340(paraxial mesoderm morphogenesis);GO:0050678(regulation of epithelial cell proliferation);GO:0050776(regulation of immune response);GO:0051098(regulation of binding)	GO:0005622(intracellular);GO:0005634(nucleus);GO:0005886(plasma membrane)	GO:0003690(double-stranded DNA binding);GO:0003700(transcription factor activity);GO:0008134(transcription factor binding);GO:0016563(transcriptional activator activity)
A_23_P48936	NM_005902	SMAD3	NM_005902	Homo sapiens SMAD family member 3 (SMAD3), mRNA [NM_005902]	chr15	GO:0000122(negative regulation of transcription from RNA polymerase II promoter);GO:0001707(mesoderm formation);GO:0006350(transcription);GO:0006366(transcription from RNA polymerase II promoter);GO:0016202(regulation of striated muscle development);GO:0017015(regulation of transforming growth factor beta receptor signaling pathway);GO:0042110(T cell activation);GO:0045944(positive regulation of transcription from RNA polymerase II promoter);GO:0048340(paraxial mesoderm morphogenesis);GO:0050678(regulation of epithelial cell proliferation);GO:0050776(regulation of immune response);GO:0051098(regulation of binding)	GO:0005622(intracellular);GO:0005634(nucleus);GO:0005886(plasma membrane)	GO:0003690(double-stranded DNA binding);GO:0003700(transcription factor activity);GO:0008134(transcription factor binding);GO:0016563(transcriptional activator activity)
A_23_P60271	NM_006444	SMC2	NM_006444	Homo sapiens structural maintenance of chromosomes 2 (SMC2), transcript variant 3, mRNA [NM_006444]	chr9	GO:0006259(DNA metabolic process);GO:0007049(cell cycle);GO:0007067(mitosis);GO:0007076(mitotic chromosome condensation);GO:0051276(chromosome organization and biogenesis);GO:0051301(cell division)	GO:0000228(nuclear chromosome);GO:0000796(condensin complex);GO:0005634(nucleus);GO:0005694(chromosome);GO:0005737(cytoplasm)	GO:0000166(nucleotide binding);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0046982(protein heterodimerization activity)
A_23_P131846	NM_005985	SNAI1	NM_005985	Homo sapiens snail homolog 1 (Drosophila) (SNAI1), mRNA [NM_005985]	chr20	GO:0001502(cartilage condensation);GO:0007275(multicellular organismal development);GO:0007399(nervous system development)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003677(DNA binding);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P160720	NM_018664	SNFT	NM_018664	Homo sapiens Jun dimerization protein p21SNFT (SNFT), mRNA [NM_018664]	chr1	GO:0006355(regulation of transcription, DNA-dependent);GO:0006366(transcription from RNA polymerase II promoter)	GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0003714(transcription corepressor activity);GO:0046983(protein dimerization activity)
A_24_P498767	BM926530	SNHG8	BM926530	AGENCOURT_6644733 NIH_MGC_122 Homo sapiens cDNA clone IMAGE:5766924 5', mRNA sequence [BM926530]	chr4			
A_23_P207058	NM_003955	SOCS3	NM_003955	Homo sapiens suppressor of cytokine signaling 3 (SOCS3), mRNA [NM_003955]	chr17	GO:0001558(regulation of cell growth);GO:0001932(regulation of protein amino acid phosphorylation);GO:0006916(anti-apoptosis);GO:0007242(intracellular signaling cascade);GO:0007259(JAK-STAT cascade);GO:0046627(negative regulation of insulin receptor signaling pathway)		GO:0004860(protein kinase inhibitor activity);GO:0005515(protein binding)
A_23_P25615	NM_017826	SOHLH2	NM_017826	Homo sapiens spermatogenesis and oogenesis specific basic helix-loop-helix 2 (SOHLH2), mRNA [NM_017826]	chr13	GO:0045449(regulation of transcription)	GO:0005634(nucleus)	GO:0030528(transcription regulator activity)
A_23_P89509	NM_006461	SPAG5	NM_006461	Homo sapiens sperm associated antigen 5 (SPAG5), mRNA [NM_006461]	chr17	GO:0007049(cell cycle);GO:0007051(spindle organization and biogenesis);GO:0007067(mitosis);GO:0048015(phosphoinositide-mediated signaling);GO:0051301(cell division)	GO:0005876(spindle microtubule)	
A_23_P81399	NM_003900	SQSTM1	NM_003900	Homo sapiens sequestosome 1 (SQSTM1), mRNA [NM_003900]	chr5	GO:0006511(ubiquitin-dependent protein catabolic process);GO:0006915(apoptosis);GO:0006950(response to stress);GO:0006955(immune response);GO:0007242(intracellular signaling cascade);GO:0008104(protein localization);GO:0016197(endosome transport);GO:0030154(cell differentiation);GO:0043122(regulation of I-kappaB kinase/NF-kappaB cascade);GO:0045944(positive regulation of transcription from RNA polymerase II promoter)	GO:0005634(nucleus);GO:0005829(cytosol)	GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0019901(protein kinase binding);GO:0030971(receptor tyrosine kinase binding);GO:0042169(SH2 domain binding);GO:0043130(ubiquitin binding);GO:0046872(metal ion binding)
A_23_P320113	NM_080725	SRXN1	NM_080725	Homo sapiens sulfiredoxin 1 homolog (S. cerevisiae) (SRXN1), mRNA [NM_080725]	chr20	GO:0006979(response to oxidative stress)	GO:0005829(cytosol)	GO:0000166(nucleotide binding);GO:0000287(magnesium ion binding);GO:0005524(ATP binding);GO:0016209(antioxidant activity);GO:0016667(oxidoreductase activity, acting on sulfur group of donors)
A_24_P244706	NM_001049	SSTR1	NM_001049	Homo sapiens somatostatin receptor 1 (SSTR1), mRNA [NM_001049]	chr14	GO:0007187(G-protein signaling, coupled to cyclic nucleotide second messenger);GO:0007215(glutamate signaling pathway);GO:0007218(neuropeptide signaling pathway);GO:0007267(cell-cell signaling);GO:0007584(response to nutrient);GO:0007586(digestion);GO:0008285(negative regulation of cell proliferation)	GO:0005624(membrane fraction);GO:0005886(plasma membrane);GO:0005887(integral to plasma membrane)	GO:0001584(rhodopsin-like receptor activity);GO:0004872(receptor activity);GO:0004994(somatostatin receptor activity)

A_23_P201376	NM_014021	SSX2IP	NM_014021	Homo sapiens synovial sarcoma, X breakpoint 2 interacting protein (SSX2IP), mRNA [NM_014021]	chr1	GO:0007155(cell adhesion)	GO:0005634(nucleus);GO:0043234(protein complex)	GO:0005515(protein binding)
A_23_P385322	NM_020799	STAMBPL1	NM_020799	Homo sapiens STAM binding protein-like 1 (STAMBPL1), mRNA [NM_020799]	chr10	GO:0006512(ubiquitin cycle)		GO:0004221(ubiquitin thiolesterase activity);GO:0008237(metallopeptidase activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_24_P99046	NM_015000	STK38L	NM_015000	Homo sapiens serine/threonine kinase 38 like (STK38L), mRNA [NM_015000]	chr12	GO:0006468(protein amino acid phosphorylation);GO:0007243(protein kinase cascade);GO:0051128(regulation of cellular component organization and biogenesis)	GO:0005737(cytoplasm);GO:0015629(actin cytoskeleton)	GO:0000166(nucleotide binding);GO:0000287(magnesium ion binding);GO:0003779(actin binding);GO:0004674(protein serine/threonine kinase activity);GO:0005515(protein binding);GO:0005524(ATP binding);GO:0016740(transferase activity)
A_23_P165927	NM_015894	STMN3	NM_015894	Homo sapiens stathmin-like 3 (STMN3), mRNA [NM_015894]	chr20	GO:0007242(intracellular signaling cascade);GO:0007399(nervous system development)		
A_24_P928068	BC048985	TAF15	BC048985	Homo sapiens TAF15 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 68kDa, mRNA (cDNA clone IMAGE:5266186). [BC048985]	chr17		GO:0005622(intracellular);GO:0005634(nucleus);GO:00056 69(transcription factor TFIID complex)	GO:0003677(DNA binding);GO:0003697(single-stranded DNA binding);GO:0003702(RNA polymerase II transcription factor activity);GO:0003727(single-stranded RNA binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P44993	NM_006755	TALDO1	NM_006755	Homo sapiens transaldolase 1 (TALDO1), mRNA [NM_006755]	chr11	GO:0005975(carbohydrate metabolic process);GO:0006098(pentose-phosphate shunt);GO:0008152(metabolic process)	GO:0005737(cytoplasm)	GO:0003824(catalytic activity);GO:0004801(transaldolase activity);GO:0005515(protein binding);GO:0016740(transferase activity)
A_23_P393620	NM_006528	TFPI2	NM_006528	Homo sapiens tissue factor pathway inhibitor 2 (TFPI2), mRNA [NM_006528]	chr7	GO:0007596(blood coagulation)	GO:0005576(extracellular region);GO:0005578(proteinaceous extracellular matrix)	GO:0004867(serine-type endopeptidase inhibitor activity);GO:0005201(extracellular matrix structural constituent)
A_24_P95070	ENST00000222543	TFPI2		Tissue factor pathway inhibitor 2 precursor (TFPI-2) (Placental protein 5) (PP5). [Source:Uniprot/SWISSPROT;Acc:P48307] [ENST00000222543]	chr7	GO:0007596(blood coagulation)	GO:0005576(extracellular region);GO:0005578(proteinaceous extracellular matrix)	GO:0004867(serine-type endopeptidase inhibitor activity);GO:0005201(extracellular matrix structural constituent)
A_32_P172920	THC2500237	THC2500237		CB027_HUMAN (Q580R0) Protein C2orf27, partial (79%) [THC2500237]	chr2			
A_32_P24059	THC2525418	THC2525418		Q53H12_HUMAN (Q53H12) Multi-substrate lipid kinase variant (Fragment), partial (8%) [THC2527098]	chr7			
A_32_P91491	THC2618570	THC2618570			chr3			
A_23_P153958	THC2651501	THC2651501			chr2			
A_32_P17364	THC2664263	THC2664263			chr10			
A_32_P218671	THC2672257	THC2672257			chr10			
A_32_P35452	THC2673108	THC2673108		HSCLOCK17 clock {Homo sapiens} (exp=-1; wgp=0; cg=0), partial (3%) [THC2673108]	chr4			
A_32_P28828	THC2674068	THC2674068		Q4S8B2_TETNG (Q4S8B2) Chromosome undetermined SCAF14706, whole genome shotgun sequence, partial (6%) [THC2674068]	chr6			
A_32_P11969	THC2694800	THC2694800		Q8IVR2_HUMAN (Q8IVR2) APOLD1 protein (Fragment), partial (18%) [THC2694800]	chr12			
A_23_P123463	NM_153332	THEX1	NM_153332	Homo sapiens three prime histone mRNA exonuclease 1 (THEX1), mRNA [NM_153332]	chr8		GO:0005622(intracellular)	GO:0000287(magnesium ion binding);GO:0003723(RNA binding);GO:0008408(3'-5' exonuclease activity);GO:0016787(hydrolase activity)
A_23_P53276	NM_003920	TIMELESS	NM_003920	Homo sapiens timeless homolog (Drosophila) (TIMELESS), mRNA [NM_003920]	chr12	GO:0002009(morphogenesis of an epithelium);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0007275(multicellular organismal development);GO:0007623(circadian rhythm);GO:0009582(detection of abiotic stimulus);GO:0016481(negative regulation of transcription);GO:0030324(lung development)	GO:0005634(nucleus)	GO:0005515(protein binding);GO:0042803(protein homodimerization activity);GO:0046982(protein heterodimerization activity)
A_24_P201153	NM_201629	TJP2	NM_201629	Homo sapiens tight junction protein 2 (zona occludens 2) (TJP2), transcript variant 2, mRNA [NM_201629]	chr9		GO:0005634(nucleus);GO:0005887(integral to plasma membrane);GO:0005923(tight junction);GO:0016020(membrane)	GO:0004385(guanylate kinase activity);GO:0005515(protein binding)
A_32_P41070	NM_015008	TMCC1	NM_015008	Homo sapiens transmembrane and coiled-coil domain family 1 (TMCC1), transcript variant 2, mRNA [NM_015008]	chr3		GO:0016020(membrane);GO:0016021(integral to membrane)	
A_23_P15450	NM_018286	TMEM100	NM_018286	Homo sapiens transmembrane protein 100 (TMEM100), mRNA [NM_018286]	chr17		GO:0016020(membrane);GO:0016021(integral to membrane)	
A_23_P204158	NM_032814	TMEM118	NM_032814	Homo sapiens transmembrane protein 118 (TMEM118), mRNA [NM_032814]	chr12	GO:0006118(electron transport)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0009055(electron carrier activity);GO:0046872(metal ion binding)
A_23_P142424	NM_024660	TMEM149	NM_024660	Homo sapiens transmembrane protein 149 (TMEM149), mRNA [NM_024660]	chr19		GO:0016021(integral to membrane)	
A_24_P261125	NM_013390	TMEM2	NM_013390	Homo sapiens transmembrane protein 2 (TMEM2), mRNA [NM_013390]	chr9		GO:0016021(integral to membrane)	

A_23_P73982	NM_018087	TMEM48	NM_018087	Homo sapiens transmembrane protein 48 (TMEM48), mRNA [NM_018087]	chr1	GO:0006605(protein targeting);GO:0015031(protein transport);GO:0031081(nuclear pore distribution);GO:0051028(mRNA transport);GO:0051292(nuclear pore complex assembly)	GO:0005634(nucleus);GO:0005643(nuclear pore);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0017056(structural constituent of nuclear pore)
A_24_P222184	AK091439	TMEM48	AK091439	Homo sapiens cDNA FLJ34120 fis, clone FCBBF3009541. [AK091439]	chr1	GO:0006605(protein targeting);GO:0015031(protein transport);GO:0031081(nuclear pore distribution);GO:0051028(mRNA transport);GO:0051292(nuclear pore complex assembly)	GO:0005634(nucleus);GO:0005643(nuclear pore);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0017056(structural constituent of nuclear pore)
A_23_P57089	NM_020182	TMEPAI	NM_020182	Homo sapiens transmembrane, prostate androgen induced RNA (TMEPAI), transcript variant 1, mRNA [NM_020182]	chr20	GO:0030521(androgen receptor signaling pathway)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0003674(molecular_function);GO:0005515(protein binding)
A_24_P413126	NM_020182	TMEPAI	NM_020182	Homo sapiens transmembrane, prostate androgen induced RNA (TMEPAI), transcript variant 1, mRNA [NM_020182]	chr20	GO:0030521(androgen receptor signaling pathway)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0003674(molecular_function);GO:0005515(protein binding)
A_23_P137173	NM_021992	TMSL8	NM_021992	Homo sapiens thymosin-like 8 (TMSL8), mRNA [NM_021992]	chrX	GO:0007010(cytoskeleton organization and biogenesis);GO:0008150(biological_process)	GO:0005737(cytoplasm);GO:0005856(cytoskeleton)	GO:0003674(molecular_function);GO:0003779(actin binding)
A_24_P375485	NM_207381	TNFAIP8L3	NM_207381	Homo sapiens tumor necrosis factor, alpha-induced protein 8-like 3 (TNFAIP8L3), mRNA [NM_207381]	chr15			
A_23_P123413	NM_014729	TOX	NM_014729	Homo sapiens thymocyte selection-associated high mobility group box (TOX), mRNA [NM_014729]	chr8	GO:0006355(regulation of transcription, DNA-dependent)	GO:0000785(chromatin);GO:0005634(nucleus)	GO:0003677(DNA binding)
A_24_P226755	NM_014729	TOX	NM_014729	Homo sapiens thymocyte selection-associated high mobility group box (TOX), mRNA [NM_014729]	chr8	GO:0006355(regulation of transcription, DNA-dependent)	GO:0000785(chromatin);GO:0005634(nucleus)	GO:0003677(DNA binding)
A_23_P31143	NM_001003395	TPD52L1	NM_001003395	Homo sapiens tumor protein D52-like 1 (TPD52L1), transcript variant 2, mRNA [NM_001003395]	chr6	GO:0000086(G2/M transition of mitotic cell cycle);GO:0006309(DNA fragmentation during apoptosis);GO:0006917(induction of apoptosis);GO:0043406(positive regulation of MAPK activity);GO:0046330(positive regulation of JNK cascade)	GO:0005737(cytoplasm);GO:0048471(perinuclear region of cytoplasm)	GO:0005515(protein binding);GO:0008656(caspase activator activity);GO:0042803(protein homodimerization activity);GO:0046982(protein heterodimerization activity)
A_23_P129903	NM_006470	TRIM16	NM_006470	Homo sapiens tripartite motif-containing 16 (TRIM16), mRNA [NM_006470]	chr17		GO:0005622(intracellular);GO:0005737(cytoplasm)	GO:0003700(transcription factor activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P356526	NM_033092	TRIM5	NM_033092	Homo sapiens tripartite motif-containing 5 (TRIM5), transcript variant gamma, mRNA [NM_033092]	chr11	GO:0006512(ubiquitin cycle);GO:0009615(response to virus)	GO:0005622(intracellular)	GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0016874(ligase activity);GO:0046872(metal ion binding)
A_23_P150935	NM_005480	TROAP	NM_005480	Homo sapiens trophinin associated protein (tastin) (TROAP), mRNA [NM_005480]	chr12	GO:0007155(cell adhesion)	GO:0005737(cytoplasm)	GO:0005515(protein binding)
A_23_P217688	NM_004089	TSC22D3	NM_004089	Homo sapiens TSC22 domain family, member 3 (TSC22D3), transcript variant 2, mRNA [NM_004089]	chrX	GO:0006355(regulation of transcription, DNA-dependent);GO:0006916(anti-apoptosis)		GO:0003700(transcription factor activity)
A_23_P168610	NM_014399	TSPAN13	NM_014399	Homo sapiens tetraspanin 13 (TSPAN13), mRNA [NM_014399]	chr7		GO:0005624(membrane fraction);GO:0005887(integral to plasma membrane);GO:0016020(membrane)	
A_32_P7015	NM_012339	TSPAN15	NM_012339	Homo sapiens tetraspanin 15 (TSPAN15), mRNA [NM_012339]	chr10		GO:0005624(membrane fraction);GO:0005887(integral to plasma membrane);GO:0016020(membrane)	
A_23_P259586	NM_003318	TTK	NM_003318	Homo sapiens TTK protein kinase (TTK), mRNA [NM_003318]	chr6	GO:0000074(regulation of progression through cell cycle);GO:0006468(protein amino acid phosphorylation);GO:0007052(mitotic spindle organization and biogenesis);GO:0007094(mitotic spindle checkpoint);GO:0008284(positive regulation of cell proliferation)	GO:0005819(spindle)	GO:0000166(nucleotide binding);GO:0004674(protein serine/threonine kinase activity);GO:0004713(protein-tyrosine kinase activity);GO:0005524(ATP binding);GO:0016301(kinase activity);GO:0016740(transferase activity)
A_23_P50096	NM_001071	TYMS	NM_001071	Homo sapiens thymidylate synthetase (TYMS), mRNA [NM_001071]	chr18	GO:0006139(nucleobase, nucleoside, nucleotide and nucleic acid metabolic process);GO:0006231(dTMP biosynthetic process);GO:0006260(DNA replication);GO:0006281(DNA repair);GO:0009157(deoxyribonucleoside monophosphate biosynthetic process);GO:0009165(nucleotide biosynthetic process);GO:0048015(phosphoinositide-mediated signaling)		GO:0004799(thymidylate synthase activity);GO:0008168(methyltransferase activity);GO:0016740(transferase activity)
A_32_P171328	NM_014501	UBE2S	NM_014501	Homo sapiens ubiquitin-conjugating enzyme E2S (UBE2S), mRNA [NM_014501]	chr19	GO:0006464(protein modification process);GO:0006512(ubiquitin cycle)		GO:0004842(ubiquitin-protein ligase activity);GO:0016874(ligase activity);GO:0019787(small conjugating protein ligase activity)
A_23_P115482	NM_014176	UBE2T	NM_014176	Homo sapiens ubiquitin-conjugating enzyme E2T (putative) (UBE2T), mRNA [NM_014176]	chr1	GO:0006464(protein modification process);GO:0006512(ubiquitin cycle)		GO:0004842(ubiquitin-protein ligase activity);GO:0016874(ligase activity)
A_23_P162589	NM_001017535	VDR	NM_001017535	Homo sapiens vitamin D (1,25-dihydroxyvitamin D3) receptor (VDR), transcript variant 2, mRNA [NM_001017535]	chr12	GO:0001501(skeletal development);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006816(calcium ion transport);GO:0006874(calcium ion homeostasis);GO:0007165(signal transduction);GO:0007275(multicellular organismal development);GO:0009887(organ morphogenesis);GO:0016481(negative regulation of transcription);GO:0050892(intestinal absorption)	GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0003707(steroid hormone receptor activity);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0008434(vitamin D3 receptor activity);GO:0046872(metal ion binding)

A_23_P167096	NM_005429	VEGFC	NM_005429	Homo sapiens vascular endothelial growth factor C (VEGFC), mRNA [NM_005429]	chr4	GO:0000074(regulation of progression through cell cycle);GO:0001525(angiogenesis);GO:0006929(substrate-bound cell migration);GO:0007165(signal transduction);GO:0007275(multicellular organismal development);GO:0008283(cell proliferation);GO:0008284(positive regulation of cell proliferation);GO:0009887(organ morphogenesis);GO:0016331(morphogenesis of embryonic epithelium);GO:0030154(cell differentiation)	GO:0016020(membrane)	GO:0008083(growth factor activity)
A_23_P76761	NM_003384	VRK1	NM_003384	Homo sapiens vaccinia related kinase 1 (VRK1), mRNA [NM_003384]	chr14	GO:0006468(protein amino acid phosphorylation)		GO:0000166(nucleotide binding);GO:0004674(protein serine/threonine kinase activity);GO:0005524(ATP binding);GO:0016740(transferase activity)
A_23_P143535	NM_033661	WDR4	NM_033661	Homo sapiens WD repeat domain 4 (WDR4), transcript variant 2, mRNA [NM_033661]	chr21	GO:0008033(tRNA processing);GO:0008150(biological_process)	GO:0005575(cellular_component)	GO:0003674(molecular_function)
A_23_P211302	NM_033661	WDR4	NM_033661	Homo sapiens WD repeat domain 4 (WDR4), transcript variant 2, mRNA [NM_033661]	chr21	GO:0008033(tRNA processing);GO:0008150(biological_process)	GO:0005575(cellular_component)	GO:0003674(molecular_function)
A_23_P212284	NM_015426	WDR51A	NM_015426	Homo sapiens WD repeat domain 51A (WDR51A), mRNA [NM_015426]	chr3			
A_24_P354300	NM_015426	WDR51A	NM_015426	Homo sapiens WD repeat domain 51A (WDR51A), mRNA [NM_015426]	chr3			
A_24_P254705	NM_020394	ZNF695	NM_020394	Homo sapiens zinc finger protein 695 (ZNF695), mRNA [NM_020394]	chr1	GO:0006355(regulation of transcription, DNA-dependent)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003676(nucleic acid binding)
A_23_P135826	AK096342	ZNF93	AK096342	Homo sapiens cDNA FLJ39023 fis, clone NT2RP7004348, highly similar to ZINC FINGER PROTEIN 93. [AK096342]	chr19	GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent)	GO:0005622(intracellular);GO:0005634(nucleus)	GO:0003676(nucleic acid binding);GO:0003700(transcription factor activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P63789	NM_001005414	ZWINT	NM_001005414	Homo sapiens ZW10 interactor (ZWINT), transcript variant 4, mRNA [NM_001005414]	chr10	GO:0000070(mitotic sister chromatid segregation);GO:0007049(cell cycle);GO:0007051(spindle organization and biogenesis);GO:0007093(mitotic checkpoint);GO:0048015(phosphoinositide-mediated signaling);GO:0051301(cell division)	GO:0000776(kinetochore);GO:0005634(nucleus)	GO:0047485(protein N-terminus binding)

APPENDIX E

MECHANORESPONSE MODELING

E.1 MSC Mechanoresponses: Cyclic Strain vs. Shear Stress

E.1.1 List of shared conserved force-responsive molecules

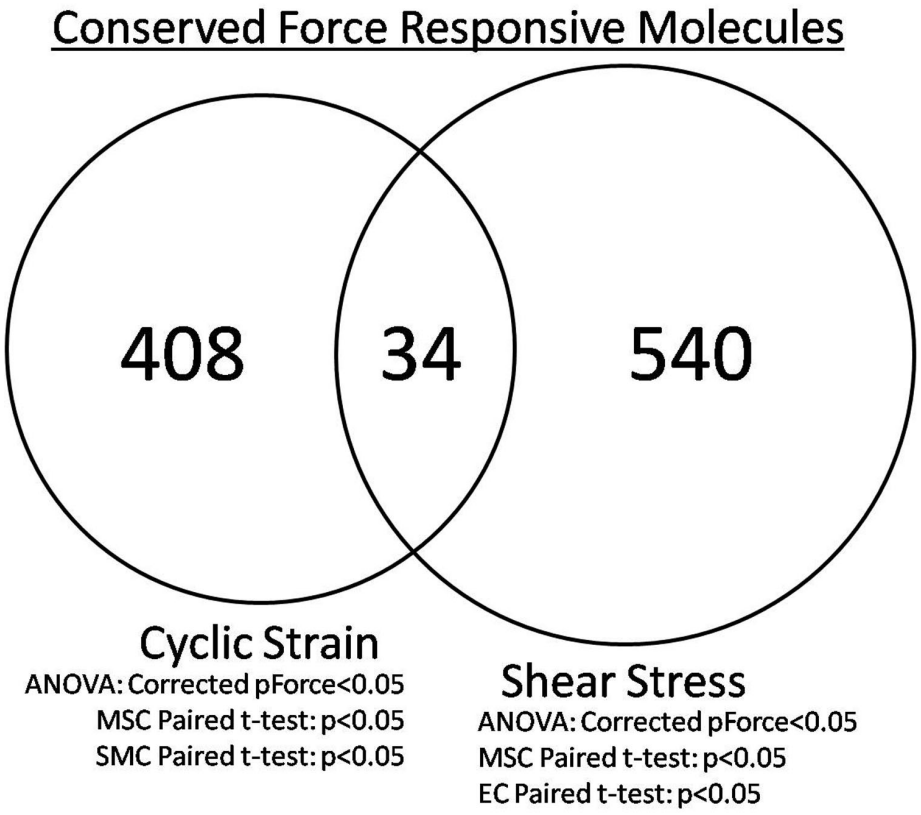


Figure 45: Genes with conserved responses to strain and shear stress. Venn diagram showing overlap between lists of conserved force-responsive genes, generated using microarray data for either cyclic strain (Chapter 4) or shear stress (Chapter 6).

Selection criteria: Shear Stress: ANOVA corrected pForce<0.05; EC paired t-test p<0.05; MSC paired t-test p<0.05; Cyclic Strain: ANOVA corrected pForce<0.05; SMC paired ttest p<0.05; MSC paired t-test p<0.05 - 34 probes								
Probe Name	**Common name**	**Gene Symbol**	**Genbank Accession**	**Description**	**Chromosome No. (Avadis)**	**GO biological process**	**GO cellular component**	**GO molecular function**
A_23_P103996	NM_002061	GCLM	NM_002061	Homo sapiens glutamate-cysteine ligase, modifier subunit (GCLM), mRNA [NM_002061]	chr1	GO:0006534(cysteine metabolic process);GO:0006536(glutamate metabolic process);GO:0006750(glutathione biosynthetic process);GO:0006979(response to oxidative stress);GO:0035229(positive regulation of glutamate-cysteine ligase activity);GO:0042493(response to drug);GO:0050880(regulation of blood vessel size)	GO:0005625(soluble fraction);GO:0005829(cytosol);GO:0017109(glutamate-cysteine ligase complex)	GO:0004357(glutamate-cysteine ligase activity);GO:0005515(protein binding);GO:0016491(oxidoreductase activity);GO:0016874(ligase activity);GO:0035226(glutamate-cysteine ligase catalytic subunit binding);GO:0046982(protein heterodimerization activity)
A_32_P177953	*ENST00000370238*	*GCLM*		*Glutamate--cysteine ligase regulatory subunit (EC 6.3.2.2) (Gamma-glutamylcysteine synthetase) (Gamma-ECS) (GCS light chain) (Glutamate--cysteine ligase modifier subunit). [Source:Uniprot/SWISSPROT;Acc:P48507] [ENST00000370238]*	*chr1*	*GO:0006534(cysteine metabolic process);GO:0006536(glutamate metabolic process);GO:0006749(glutathione metabolic process);GO:0006750(glutathione biosynthetic process);GO:0006979(response to oxidative stress);GO:0035229(positive regulation of glutamate-cysteine ligase activity);GO:0042493(response to drug);GO:0050880(regulation of blood vessel size)*	*GO:0005625(soluble fraction);GO:0005829(cytosol);GO:0017109(glutamate-cysteine ligase complex)*	*GO:0004357(glutamate-cysteine ligase activity);GO:0005515(protein binding);GO:0016491(oxidoreductase activity);GO:0016874(ligase activity);GO:0035226(glutamate-cysteine ligase catalytic subunit binding);GO:0046982(protein heterodimerization activity)*
A_23_P39766	NM_014905	GLS	NM_014905	Homo sapiens glutaminase (GLS), mRNA [NM_014905]	chr2	GO:0006543(glutamine catabolic process)	GO:0005739(mitochondrion)	GO:0004359(glutaminase activity);GO:0016787(hydrolase activity)
A_23_P136724	BX640843	LOC344887	BX640843	Homo sapiens mRNA; cDNA DKFZp686B14224 (from clone DKFZp686B14224). [BX640843]	chr3			
A_23_P21473	NM_024491	CEP70	NM_024491	Homo sapiens centrosomal protein 70kDa (CEP70), mRNA [NM_024491]	chr3			
A_23_P6771	NM_014583	LMCD1	NM_014583	Homo sapiens LIM and cysteine-rich domains 1 (LMCD1), mRNA [NM_014583]	chr3	GO:0000122(negative regulation of transcription from RNA polymerase II promoter);GO:0008150(biological_process)	GO:0005575(cellular_component);GO:0005634(nucleus)	GO:0003674(molecular_function);GO:0003714(transcription corepressor activity);GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_24_P68908	BX640843	LOC344887	BX640843	Homo sapiens mRNA; cDNA DKFZp686B14224 (from clone DKFZp686B14224). [BX640843]	chr3			
A_23_P255331	NM_032623	OSAP	NM_032623	Homo sapiens ovary-specific acidic protein (OSAP), mRNA [NM_032623]	chr4			
A_23_P426021	NM_015187	KIAA0746	NM_015187	Homo sapiens KIAA0746 protein (KIAA0746), mRNA [NM_015187]	chr4			GO:0005488(binding)
A_23_P58328	NM_007193	ANXA10	NM_007193	Homo sapiens annexin A10 (ANXA10), mRNA [NM_007193]	chr4		GO:0005739(mitochondrion)	GO:0005509(calcium ion binding);GO:0005544(calcium-dependent phospholipid binding)
A_32_P165477	NM_014331	SLC7A11	NM_014331	Homo sapiens solute carrier family 7, (cationic amino acid transporter, y+ system) member 11 (SLC7A11), mRNA [NM_014331]	chr4	GO:0006461(protein complex assembly);GO:0006810(transport);GO:0006865(amino acid transport)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0015171(amino acid transporter activity);GO:0015327(cystine:glutamate antiporter activity);GO:0015359(amino acid permease activity)
A_32_P42684	*NM_014331*	*SLC7A11*	*NM_014331*	*Homo sapiens solute carrier family 7, (cationic amino acid transporter, y+ system) member 11 (SLC7A11), mRNA [NM_014331]*	*chr4*	*GO:0006461(protein complex assembly);GO:0006810(transport);GO:0006865(amino acid transport)*	*GO:0016020(membrane);GO:0016021(integral to membrane)*	*GO:0015171(amino acid transporter activity);GO:0015327(cystine:glutamate antiporter activity);GO:0015359(amino acid permease activity)*
A_32_P4882	A_32_P4882	A_32_P4882			chr4			
A_23_P81399	NM_003900	SQSTM1	NM_003900	Homo sapiens sequestosome 1 (SQSTM1), mRNA [NM_003900]	chr5	GO:0006511(ubiquitin-dependent protein catabolic process);GO:0006915(apoptosis);GO:0006950(response to stress);GO:0006955(immune response);GO:0007242(intracellular signaling cascade);GO:0008104(protein localization);GO:0016197(endosome transport);GO:0030154(cell differentiation);GO:0043122(regulation of I-kappaB kinase/NF-kappaB cascade);GO:0045944(positive regulation of transcription from RNA polymerase II promoter)	GO:0005634(nucleus);GO:0005829(cytosol)	GO:0005515(protein binding);GO:0008270(zinc ion binding);GO:0019901(protein kinase binding);GO:0030971(receptor tyrosine kinase binding);GO:0042169(SH2 domain binding);GO:0043130(ubiquitin binding);GO:0046872(metal ion binding)
A_23_P31073	NM_005375	MYB	NM_005375	Homo sapiens v-myb myeloblastosis viral oncogene homolog (avian) (MYB), mRNA [NM_005375]	chr6	GO:0006355(regulation of transcription, DNA-dependent);GO:0006397(mRNA processing);GO:0007049(cell cycle);GO:0008380(RNA splicing);GO:0045449(regulation of transcription)	GO:0005634(nucleus);GO:0005681(spliceosome);GO:0016363(nuclear matrix)	GO:0003677(DNA binding);GO:0005515(protein binding);GO:0016563(transcriptional activator activity);GO:0030528(transcription regulator activity)
A_23_P372834	NM_198098	AQP1	NM_198098	Homo sapiens aquaporin 1 (Colton blood group) (AQP1), mRNA [NM_198098]	chr7	GO:0006810(transport);GO:0006833(water transport);GO:0007588(excretion)	GO:0005887(integral to plasma membrane);GO:0016020(membrane);GO:0016021(integral to membrane);GO:0019867(outer membrane)	GO:0005215(transporter activity);GO:0005372(water transporter activity);GO:0015288(porin activity)
A_23_P93938	ENST00000258775	NACAD		Homo sapiens mRNA for KIAA0363 gene, partial cds. [AB002361]	chr7	GO:0015031(protein transport)	GO:0005634(nucleus)	
A_23_P33511	AX721087	AX721087	AX721087	Sequence 47 from Patent WO0220754. [AX721087]	chr8			
A_23_P112481	NM_004925	AQP3	NM_004925	Homo sapiens aquaporin 3 (Gill blood group) (AQP3), mRNA [NM_004925]	chr9	GO:0006810(transport);GO:0007588(excretion)	GO:0005624(membrane fraction);GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0005215(transporter activity)
A_23_P158976	NM_000392	ABCC2	NM_000392	Homo sapiens ATP-binding cassette, sub-family C (CFTR/MRP), member 2 (ABCC2), mRNA [NM_000392]	chr10	GO:0006810(transport)	GO:0005887(integral to plasma membrane);GO:0016020(membrane)	GO:0000166(nucleotide binding);GO:0005215(transporter activity);GO:0005524(ATP binding);GO:0008514(organic anion transporter activity);GO:0016887(ATPase activity);GO:0042626(ATPase activity, coupled to transmembrane movement of substances)
A_23_P370682	NM_138456	BATF2	NM_138456	Homo sapiens basic leucine zipper transcription factor, ATF-like 2 (BATF2), mRNA [NM_138456]	chr11	GO:0006355(regulation of transcription, DNA-dependent)	GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0046983(protein dimerization activity)
A_23_P44993	NM_006755	TALDO1	NM_006755	Homo sapiens transaldolase 1 (TALDO1), mRNA [NM_006755]	chr11	GO:0005975(carbohydrate metabolic process);GO:0006098(pentose-phosphate shunt);GO:0008152(metabolic process)	GO:0005737(cytoplasm)	GO:0003824(catalytic activity);GO:0004801(transaldolase activity);GO:0005515(protein binding);GO:0016740(transferase activity)
A_24_P503669	AK093628	AK093628	AK093628	Homo sapiens cDNA FLJ36309 fis, clone THYMU2004986. [AK093628]	chr15			
A_23_P77415	NM_013370	OSGIN1	NM_013370	Homo sapiens oxidative stress induced growth inhibitor 1 (OSGIN1), transcript variant 1, mRNA [NM_013370]	chr16	GO:0007275(multicellular organismal development);GO:0030154(cell differentiation);GO:0030308(negative regulation of cell growth)	GO:0005575(cellular_component)	GO:0008083(growth factor activity)
A_23_P129903	NM_006470	TRIM16	NM_006470	Homo sapiens tripartite motif-containing 16 (TRIM16), mRNA [NM_006470]	chr17		GO:0005622(intracellular);GO:0005737(cytoplasm)	GO:0003700(transcription factor activity);GO:0008270(zinc ion binding);GO:0046872(metal ion binding)
A_23_P15450	NM_018286	TMEM100	NM_018286	Homo sapiens transmembrane protein 100 (TMEM100), mRNA [NM_018286]	chr17		GO:0016020(membrane);GO:0016021(integral to membrane)	
A_23_P207507	NM_003786	ABCC3	NM_003786	Homo sapiens ATP-binding cassette, sub-family C (CFTR/MRP), member 3 (ABCC3), mRNA [NM_003786]	chr17	GO:0006810(transport)	GO:0005624(membrane fraction);GO:0005887(integral to plasma membrane);GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0000166(nucleotide binding);GO:0005215(transporter activity);GO:0005524(ATP binding);GO:0008514(organic anion transporter activity);GO:0016887(ATPase activity);GO:0042626(ATPase activity, coupled to transmembrane movement of substances)
A_23_P78209	NM_002359	MAFG	NM_002359	Homo sapiens v-maf musculoaponeurotic fibrosarcoma oncogene homolog G (avian) (MAFG), transcript variant 1, mRNA [NM_002359]	chr17	GO:0001701(in utero embryonic development);GO:0006350(transcription);GO:0006355(regulation of transcription, DNA-dependent);GO:0006366(transcription from RNA polymerase II promoter);GO:0030534(adult behavior);GO:0042127(regulation of cell proliferation);GO:0045604(regulation of epidermal cell differentiation)	GO:0000785(chromatin);GO:0005634(nucleus)	GO:0003700(transcription factor activity);GO:0046983(protein dimerization activity)
A_32_P157671	A_32_P157671	A_32_P157671			chr17			
A_23_P67198	NM_015692	CPAMD8	NM_015692	Homo sapiens C3 and PZP-like, alpha-2-macroglobulin domain containing 8 (CPAMD8), mRNA [NM_015692]	chr19			GO:0004866(endopeptidase inhibitor activity)
A_23_P320113	NM_080725	SRXN1	NM_080725	Homo sapiens sulfiredoxin 1 homolog (S. cerevisiae) (SRXN1), mRNA [NM_080725]	chr20	GO:0006979(response to oxidative stress)	GO:0005829(cytosol)	GO:0000166(nucleotide binding);GO:0000287(magnesium ion binding);GO:0005524(ATP binding);GO:0016209(antioxidant activity);GO:0016667(oxidoreductase activity, acting on sulfur group of donors)
A_23_P57089	NM_020182	TMEPAI	NM_020182	Homo sapiens transmembrane, prostate androgen induced RNA (TMEPAI), transcript variant 1, mRNA [NM_020182]	chr20	GO:0030521(androgen receptor signaling pathway)	GO:0016020(membrane);GO:0016021(integral to membrane)	GO:0003674(molecular_function);GO:0005515(protein binding)
A_23_P120883	NM_002133	HMOX1	NM_002133	Homo sapiens heme oxygenase (decycling) 1 (HMOX1), mRNA [NM_002133]	chr22	GO:0006788(heme oxidation);GO:0043123(positive regulation of I-kappaB kinase/NF-kappaB cascade)	GO:0005624(membrane fraction);GO:0005783(endoplasmic reticulum);GO:0005792(microsome)	GO:0004392(heme oxygenase (decyclizing) activity);GO:0004871(signal transducer activity);GO:0005506(iron ion binding);GO:0016491(oxidoreductase activity);GO:0046872(metal ion binding)
A_23_P155162	NM_052839	PANX2	NM_052839	Homo sapiens pannexin 2 (PANX2), mRNA [NM_052839]	chr22		GO:0005921(gap junction);GO:0016020(membrane);GO:0016021(integral to membrane)	

Figure 46: List of genes with conserved force-responses to cyclic strain and shear stress. Annotation information for genes with significant ($p < 0.05$) conserved expression level changes in response to both cyclic strain and shear stress. 34 genes intersected from the lists of conserved strain-sensitive (442 genes) and shear stress-sensitive (574 genes). Genes are listed in order of chromosome location.

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